AJHP®

American Journal of Health-System Pharmacy™

VOLUME 67 | NUMBER 15 | SUPPLEMENT 7

AUGUST 1, 2010

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SUPPLEMENT

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Official journal of the American Society of Health-System Pharmacists®

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This activity supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company

AJHP®

American Journal of Health-System Pharmacy™
Volume 67 • Number 15 • Supplement 7
www.ashp.org

Official Journal
American Society of Health-System Pharmacists®

Henri R. Manasse, Jr.
Executive Vice President

August 1, 2010

Coden: AHSPEK
ISSN: 1079-2082

Optimizing antiplatelet therapy in acute coronary syndromes: Balancing efficacy and safety in unstable angina and non-ST-segment elevation myocardial infarction

Articles based on the proceedings of a symposium held December 7, 2009, in conjunction with the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. This activity was supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company

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Management of non-ST-segment elevation acute coronary syndromes Introduction

SANDEEP NATHAN

Am J Health-Syst Pharm. 2010; 67(Suppl 7):S3-6

While it was once believed that the primary physiological function of platelets was mediation of cellular hemostasis, it is now understood that activated platelets have a crucial role in the pathobiology of a variety of processes, including inflammation, leukocyte adhesion, progression of atherosclerosis, and pathological vascular thrombosis.[1] Fundamentally, acute coronary syndromes (ACS) may be regarded as platelet-centric diseases, as it has been demonstrated that activation and aggregation of platelets play central roles in the genesis of ACS.

Platelet activation comprises a complex cascade involving multiple interwoven biological processes and distinct mechanisms.[2] Vascular injury resulting from spontaneous rupture of a vulnerable atherosclerotic plaque or iatrogenic disruption of the vascular endothelium due to percutaneous coronary intervention (PCI) leads to activation of the coagulation and platelet cascades. Acute vascular injury exposes subendothelial collagen and tissue factor to the circulating blood pool. Platelets adhere to the exposed subendothelium through the interaction of bound proteins with a variety of platelet surface receptors. Importantly, von Willebrand factor participates in the initial tethering sequence via binding of the platelet surface glycoprotein (GP) Ib/V/IX receptor complex. Collagen interacts similarly with GPs VI and Ia. Platelets become activated upon contact with collagen, as well as a variety of other agonists, with resultant secretion of platelet granule contents and aggregation via crosslinking of activated GP IIb/IIIa (integrin $\alpha_{IIb}\beta_3$) complexes with soluble fibrinogen. Once activated, platelets also acquire an enhanced capacity to catalyze interactions between activated coagulation factors, thus promoting the generation of thrombin, which, in turn, converts the soluble protein fibrinogen to fibrin, resulting in thrombus formation.[1,3] Exposed tissue factor independently triggers the generation of minute amounts of thrombin (Factor IIa), which, in turn, results in a subsequent explosive generation of thrombin and further platelet activation.[2,4-6] Via degranulation, the activated platelet also releases a variety of agonists, such as adenosine diphosphate (ADP) and thromboxane A_2, which further amplify platelet activation and aggregation. The net result is a cycle of vascular injury, inflammation, and occlusion, in which coagulation factor assembly and activation occurs in a complementary and synergistic fashion with platelet activation and aggregation.[2,5]

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Based on the proceedings of a symposium held December 7, 2009, in conjunction with the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company.

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DOI 10.2146/ajhp100164

The clinical presentation of a patient with atherothrombosis is largely determined by the extent of vascular thrombosis, the degree of obstruction to coronary blood flow, and the presence or absence of collateral flow to the vascular territory involved. As such, there is considerable commonality and overlap in the pathobiology of non-ST-segment elevation ACS and ST-segment elevation myocardial infarction (STEMI). While large-scale clinical trial data would suggest a fairly broad and uniform benefit associated with antiplatelet therapy in the setting of ACS, more recent observations suggest that high on-treatment platelet reactivity is a quantifiable and modifiable risk factor for recurrent atherothrombosis in these patients. Optimal management of ACS, therefore, involves a number of considerations regarding the suppression of platelet activity (Figure 1).

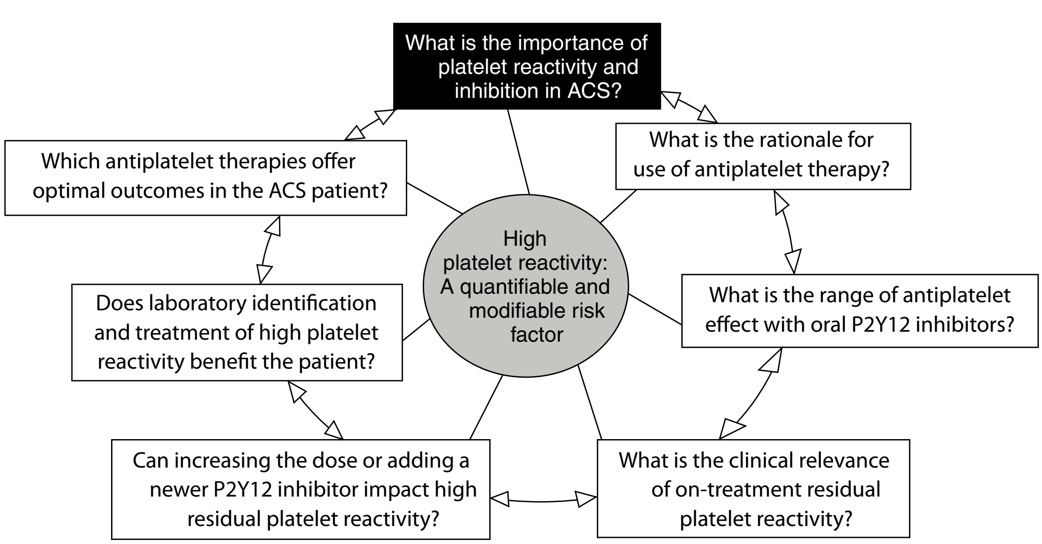
In patients with ACS, early treatment with agents that provide predictable and therapeutically adequate levels of platelet inhibition should be a primary management goal. Currently available and investigational oral antiplatelet agents target various pathways in the cascade of events that occur following vascular injury. Aspirin, an indirect thromboxane inhibitor, has been a mainstay in the management of ACS patients.[1] The potentially beneficial effects of aspirin used in this capacity include antiinflammation, antioxidation, and irreversible inhibition of the platelet cyclooxygenase (COX)-1 enzyme.[7] However, compared with other available agents, aspirin is a rather modest inhibitor of platelet aggregation, and this agent is typically used in combination with other antiplatelet drugs.

The ADP P2Y12 receptor, one of three important platelet surface purinoreceptors, appears to serve as a gateway for platelet activation, as well as conformational activation of a variety of other receptors. The P2Y12 receptor plays a role in the mediation of the GP IIb/IIIa receptor complex, as well as the protease-activated receptors (PARS) 1 and 4. Several currently available oral antiplatelet agents, along with other agents that are under investigation, bind and inhibit the P2Y12 receptor.

Clopidogrel is a thienopyridine ADP-receptor antagonist which irreversibly binds to the P2Y12 receptor. Compared with aspirin, clopidogrel monotherapy was initially shown to be more efficacious in reducing ischemic risk in stable patients with atherosclerosis.[8] Subsequent trials demonstrated a significant reduction in the number of both short-term and long-term ischemic events with the addition of clopidogrel to aspirin in ACS patients.[5] Dual antiplatelet therapy with clopidogrel and aspirin has long been considered the gold standard of oral antiplatelet therapy in secondary prevention of major cardiovascular events.[9] More recent investigations have revealed, however, that clopidogrel is associated with variable responses and a delayed onset of action (i.e., 2–6 hours for a 600-mg loading dose and 12–24 hours for a 300-mg loading dose) in a significant proportion of treated patients. These limitations have led to concerns regarding clopidogrel's efficacy and the development of more potent and predictable antiplatelet agents.[10]

Prasugrel is also a thienopyridine ADP-receptor antagonist that irreversibly binds to the P2Y12 receptor. Compared with clopidogrel, prasug-

Figure 1. Questions surrounding the management of acute coronary syndromes (ACS) with antiplatelet therapy.



rel has a more rapid onset of action (i.e., 1–2 hours for a 60-mg loading dose) and greater potency.[11] While both agents are prodrugs, more efficient conversion of prasugrel to its active metabolite relative to that of clopidogrel results in higher levels of inhibition of platelet aggregation with lower interpatient variability.[12,13] Results of clinical trials comparing prasugrel with standard-dose and high-dose clopidogrel have shown greater clinical efficacy with the use of prasugrel in ACS patients undergoing PCI.[11,14]

The investigational oral agent ticagrelor is an ADP-receptor antagonist that differs from clopidogrel and prasugrel in that it is a directly active and reversible P2Y12 inhibitor. Since ticagrelor is not a prodrug, it has a more rapid onset of action (i.e., 0.5–2 hours for a 180-mg loading dose) and yields more pronounced platelet inhibition than clopidogrel.[15,16] Evidence indicates that ticagrelor is more efficacious than clopidogrel in reducing ischemic events in patients with ACS who are being managed in a contemporary, aggressive fashion.[17] A new drug application for ticagrelor was submitted to FDA in November 2009.

The management of patients with ACS is becoming increasingly more complex with the proliferation of new therapeutic options. The American College of Cardiology and the American Heart Association have published numerous guidelines to aid in the management of patients with ACS (non-ST-segment elevation and STEMI), as well as those undergoing PCI or stent placement.[18,19] Focused updates to joint guidelines for the management of patients with STEMI/PCI were recently published, and these updated guidelines also provide recommendations for the management of unstable angina/non-STEMI patients selected for an invasive approach.[20] Health-system pharmacists must be aware of these guidelines and the benefits and risks associated with oral antiplatelet agents, and apply these insights when making recommendations for managing patients in need of antiplatelet therapy.

The first article of this supplement discusses the role of oral antiplatelet therapies in the management of ACS patients and those who have undergone PCI and stenting, as well as the importance of balancing the efficacy and risk of bleeding when using these agents. This article also reviews the major clinical trials evaluating currently available and investigational oral antiplatelet therapies for managing ACS and discusses the guidelines for antiplatelet use in various patients with ACS. The second article focuses on optimizing efficacy, managing drug interactions, and controlling bleeding risk in patients with ACS and after PCI who are receiving oral antiplatelet agents. The second article will also discuss pharmacogenetics, complications that may occur with stenting, adverse events associated with antiplatelet use, response variability, and the possible need for monitoring. The last article discusses the case of a 55-year-old woman who arrives at the emergency department after three days of progressive substernal chest pain, and will review the patient's history, differential diagnosis, and appropriate management.

References

1. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. *Circ Res*. 2007; 100:1261-75.
2. Jackson SP. The growing complexity of platelet aggregation. *Blood*. 2007; 109:5087-95.
3. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007; 357:2482-94.
4. Ruggeri ZM. Platelets in atherothrombosis. *Nat Med*. 2002; 8:1227-34.
5. Tantry US, Etherington A, Bliden KP et al. Antiplatelet therapy: current strategies and future trends. *Future Cardiol*. 2006; 2:343-66.
6. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. 2008; 359:938-49.
7. Awtry EH, Loscalzo J. Aspirin. *Circulation*. 2000; 101:1206-18.
8. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996; 348:1329-39.
9. Rossini R, Musumeci G, Nijaradze T et al. Clopidogrel bisulfate: a review of its use in the management of acute coronary syndrome. *Clin Med Ther*. 2009; 1:899-910.
10. Schomig A. Ticagrelor—is there need for a new player in the antiplatelet-therapy field? *N Engl J Med*. 2009; 361:1108-11.
11. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357:2001-15.
12. Brandt JT, Payne CD, Wiviott SD et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007; 153:66.e9-16.
13. Wiviott SD, Antman EM, Gibson CM et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J*. 2006; 152:627-35.
14. Wiviott SD, Trenk D, Frelinger AL et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007; 116:2923-32.
15. Husted S, Emanuelsson H, Heptinstall S et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006; 27:1038-47.
16. Storey RF, Husted S, Harrington RA et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007; 50:1852-6.
17. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009; 361:1045-57.
18. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physi-

cians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007; 50:e1-157.

19. King SB III, Smith SC Jr, Hirshfeld JW Jr et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2008; 51:172-209.
20. Kushner FG, Hand M, Smith SC Jr et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009; 54:2205-41.

Oral antiplatelet therapy after acute coronary syndrome and percutaneous coronary intervention: Balancing efficacy and bleeding risk

SARAH A. SPINLER

Purpose: The benefits and risk of bleeding associated with oral antiplatelet agents used for acute coronary syndrome (ACS) or in patients who have undergone percutaneous coronary intervention (PCI) are discussed.

Summary: Over the past decade, significant advances have been made with the use of oral antiplatelet agents in ACS patients and in those undergoing PCI and stenting. Dual antiplatelet therapy with clopidogrel and aspirin has been considered the gold standard for reducing cardiovascular events in these patients. However, use of clopidogrel has limitations, including variable patient response. These limitations can affect patient outcomes achieved with clopidogrel, leading to concerns regarding its use. Subsequently, more potent oral antiplatelet agents have been developed, including prasugrel and ticagrelor. Prasugrel is an oral thienopyridine with greater potency and less antiplatelet variability than clopidogrel. Ticagrelor, another oral antiplatelet agent that has shown greater platelet inhibition than clopidogrel, is currently under investigation. Although a greater reduction in ischemic events has been observed with dual antiplatelet therapy and the use of newer oral antiplatelet agents, there is also a progressive increase in the risk of major bleeding. Treatment decisions should be based on current practice guidelines, as well as individualized patient risk and benefit analyses.

Conclusion: Knowledge of the benefits and bleeding risks associated with oral antiplatelet agents, as well as guideline recommendations, can help health care providers make informed decisions regarding the most appropriate therapy for patients after ACS and PCI.

Index terms: Acute coronary syndrome; Angioplasty; Aspirin; Clopidogrel; Hemorrhage; Platelet aggregation inhibitors; Prasugrel; Protocols; Stents; Ticagrelor; Toxicity

Am J Health-Syst Pharm. 2010; 67(Suppl 7):S7-17

Antiplatelet therapies are the cornerstone of treatment for acute coronary syndromes (ACS) and following percutaneous coronary intervention (PCI) with stent implantation. In patients with ACS, dual antiplatelet therapy with clopidogrel and aspirin has been considered the gold standard for reducing cardiovascular (CV) events.[1] However, limitations have been observed with the use of clopidogrel (e.g., delayed onset of action, variable response), leading to concerns regarding its use and the subsequent development of more potent oral antiplatelet agents.[2] Prasugrel, a new oral thienopyridine with greater potency and less antiplatelet variability than clopidogrel,[3] was approved by the Food and Drug Administration (FDA) in July 2009.[4] Additionally, promising results have been observed in clinical trials of ticagrelor, another oral antiplatelet agent that has shown greater platelet inhibition compared with that of clopidogrel.[5] These new agents may lead to improved patient outcomes, as net clinical benefit has been observed with increasingly potent oral antiplatelet regimens.

As the spectrum of available oral antiplatelet agents continues to expand, health-system pharmacists are faced with formulary questions regarding the best use of these agents, including what is the most appro-

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Based on the proceedings of a symposium held December 7, 2009, in conjunction with the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company.

Dr. Spinler has served on the speakers' bureaus for Bristol-Myers Squibb, Sanofi Aventis, and Schering-Plough. She received an honorarium from Potomac Center for Medical Education (PCME) for her participation in the symposium and for her work on this article. This article was developed with the assistance of a medical writer working with PCME. Dr. Spinler approved the final article and all of its content.

 1079-2082/10/0801-00S7$06.00.
DOI 10.2146/ajhp100165

priate therapy for a specific patient, given the inclusion and exclusion criteria of comparative clinical trials balanced against bleeding risk; when and where should therapy be initiated, whether early in the emergency department or in the cardiac catheterization laboratory after the coronary anatomy is known; and, as the patient is transitioned to home, what is the optimal duration of use?[6] A greater reduction in the number of ischemic events has been observed with dual antiplatelet therapy and the use of newer oral antiplatelet agents, but these treatments have been associated with a progressive increase in the risk of major bleeding.

Oral antiplatelet therapies for ACS

In patients with ACS (ST-segment-elevation myocardial infarction [STEMI] and unstable angina [UA]/non-STEMI [NSTEMI]) and in those undergoing PCI, appropriate oral antiplatelet therapy is necessary to reduce the risk of CV death, myocardial infarction (MI), and stroke, as well as to prevent reinfarction and stent thrombosis. Currently available oral antiplatelet therapies for ACS include aspirin, clopidogrel, and prasugrel; ticagrelor is under investigation.

Guideline recommendations. Dual antiplatelet therapy with aspirin and a thienopyridine is recommended for both patients undergoing elective PCI and in patients with ACS who are being treated medically or undergoing PCI. The 2009 joint American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) STEMI/PCI focused update guidelines[7] recommend administration of either clopidogrel (300-mg or 600-mg loading dose) as early as possible before or at the time of primary or nonprimary PCI, or prasugrel (60-mg loading dose) as soon as possible for primary PCI in STEMI patients undergoing planned PCI (Class I recommendation). After stent placement, patients with ACS should receive either clopidogrel (75 mg/day) or prasugrel (10 mg/day) for at least 12 months (Class I recommendation) and for up to 15 months (Class IIb recommendation). In UA/NSTEMI patients selected for an invasive approach, these guidelines recommend administration of clopidogrel (300 mg or 600 mg) before or at the time of PCI, or prasugrel (60 mg) at the time of PCI (Class I recommendation). Therefore, for patients with STEMI undergoing primary PCI, either clopidogrel or prasugrel is recommended, administered either in the emergency department or in the cardiac catheterization laboratory. For patients undergoing PCI for UA/NSTEMI, clopidogrel may be administered either in the emergency department, hospital ward, or cardiac catheterization laboratory, and administration of prasugrel should be reserved for the cardiac catheterization laboratory after coronary anatomy is known.

In patients undergoing coronary artery bypass grafting (CABG), clopidogrel should be withheld for at least 5 days and prasugrel for at least 7 days, unless the need for revascularization, the net benefit of thienopyridine therapy, or both outweigh the potential risks of excess bleeding. The 2009 joint STEMI/PCI focused update guidelines do not explicitly recommend use of one thienopyridine over the other in patients without contraindications.[7]

The 2007 ACC/AHA guidelines for the management of UA/NSTEMI recommend administration of aspirin (162–325 mg) during PCI in patients who did not receive aspirin therapy as initial medical treatment.[8] Following PCI, aspirin (162–325 mg/day) should be continued for at least 1 month in patients with a bare-metal stent, 3 months in patients with a sirolimus stent, and 6 months in those with a paclitaxel stent, followed by aspirin (75–162 mg/day) indefinitely. In patients in whom there is a concern of bleeding, a lower dosage of aspirin (75–162 mg/day) can be used initially after PCI. In patients with definite or likely UA/NSTEMI selected for an invasive approach, the initiation of aspirin is recommended on presentation.[7]

In stable patients undergoing elective PCI, the 2007 PCI focused update recommended the use of aspirin (75–325 mg) before PCI in patients taking daily aspirin therapy.[9] Patients who are not on daily long-term aspirin therapy should receive aspirin (300–325 mg) at least 2 hours (preferably 24 hours) before PCI. After PCI, aspirin (162–325 mg/day) should be continued for at least 1 month in patients with a bare-metal stent, 3 months for a sirolimus stent, and 6 months for a paclitaxel stent, followed by aspirin (75–162 mg/day) indefinitely.

Clinical trials. Numerous studies have been undertaken to determine the optimal use of clopidogrel in patients with ACS and in those undergoing PCI. The definitions of bleeding used in these trials are provided in Appendix A.[5,10-18]

Dual antiplatelet therapy. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial evaluated the use of single antiplatelet therapy versus dual antiplatelet therapy in ACS patients without ST-segment elevation.[10] Patients who presented within 24 hours after symptom onset were randomized to receive clopidogrel (300-mg dose immediately, followed by 75 mg/day) or placebo, in addition to aspirin, for 3 to 12 months. Results demonstrated a 20% relative risk reduction in the composite outcome of nonfatal MI, stroke, or death from CV causes with the use of clopidogrel compared with placebo at 12 months ($p < 0.001$). Overall, there were 582 (9.3%) first events in the clopidogrel group and 719 (11.4%) in the placebo group ($p < 0.001$). The benefit of clopidogrel was apparent within a few hours after randomization. By 24 hours after randomization, the rate of death from CV causes, nonfatal MI, stroke, or refractory or severe ischemia was significantly lower in patients receiving clopidogrel (1.4%) compared with placebo (2.1%). Clopidogrel use was associated with an increased risk of bleeding (Appendix A). Dual antiplatelet therapy with clopidogrel and aspirin was well tolerated and improved patient outcomes compared with aspirin alone.

Clopidogrel therapy before and after PCI. The PCI-CURE trial further evaluated a subset of patients from the CURE trial who were undergoing PCI to determine whether pretreatment followed by long-term therapy with clopidogrel was superior to no pretreatment and short-term therapy.[19] Patients with NSTEMI were randomly assigned to receive double-blind treatment with clopidogrel or placebo, in addition to aspirin, for a median of 6 days before PCI. In both treatment groups, more than 80% of patients received open-label thienopyridine therapy for approximately 4 weeks after PCI. The study treatment (clopidogrel or placebo) was then restarted and continued for a mean of 8 months.

The primary endpoint of the PCI-CURE trial was a composite of MI, CV death, or urgent target-vessel revascularization within 30 days of PCI.[19] Results showed that clopidogrel use was associated with an overall relative risk reduction of 31% in CV death or MI compared with placebo ($p = 0.002$), which included events that were prevented before and after PCI. The primary endpoint occurred in 4.5% of patients receiving clopidogrel and 6.4% of those in the placebo group ($p = 0.03$). After PCI, long-term clopidogrel use was associated with a reduced rate of CV death or MI ($p = 0.047$), as well as CV death, MI, or any revascularization ($p = 0.03$). At follow-up, no significant difference in major bleeding was observed between the groups. The investigators concluded that in ACS patients who are receiving aspirin, clopidogrel pretreatment followed by long-term therapy after PCI is beneficial for reducing major CV events compared with placebo.[19]

Timing of the clopidogrel loading dose. While assessing the efficacy and safety of clopidogrel (300-mg loading dose followed by 75 mg/day for 28 days or 1 year), the Clopidogrel for the Reduction of Events During Observation (CREDO) trial investigators evaluated the timing of loading dose administration to determine if this could affect patient outcomes.[20] The mean duration between the administration of the study drug loading dose and PCI was 9.8 hours; 51% of patients received the loading dose between 3 and less than 6 hours before PCI and 49% were given the loading dose between 6 and 24 hours before PCI. Results demonstrated no treatment benefit in patients who received the clopidogrel loading dose 3 to <6 hours before PCI. However, a 38.6% relative risk reduction in the composite endpoint of death, MI, or urgent target vessel revascularization at 28 days was observed in patients who received clopidogrel pretreatment ≥6 hours before PCI ($p = 0.051$). Subgroup analyses indicate that a longer interval between the loading dose and PCI may reduce the rate of death and ischemic events.

Higher versus lower clopidogrel loading dose. Early studies of clopidogrel evaluated the use of a 300-mg loading dose. However, an earlier and stronger inhibition of adenosine diphosphate (ADP)-induced platelet activation has been observed with a 600-mg dose of clopidogrel compared with a 300-mg dose,[21] with observational data suggesting a reduction in 30-day cardiac events with the higher dose of clopidogrel.[22] Several trials have been undertaken to evaluate whether a higher loading dose of clopidogrel produces better outcomes in patients undergoing PCI.

The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2) trial evaluated the effect of a 300-mg versus a 600-mg loading dose of clopidogrel on the primary endpoint of MI, target vessel revascularization, or 30-day occurrence of death in patients undergoing PCI.[23] The investigators observed antiplatelet effects by measuring creatine kinase MB, troponin I, and myoglobin levels at baseline and at 8 and 24 hours after clopidogrel administration. In this study, the primary endpoint occurred in 4% of patients receiving the higher clopidogrel loading dose compared with 12% of those receiving the conventional loading dose ($p = 0.041$). These results were entirely due to the occurrence of periprocedural MI (15 events in the 300-mg treatment group; 5 events in the 600-mg treatment group). Multivariate analysis demonstrated a 50% reduction in the risk of MI with the high loading-dose regimen ($p = 0.044$). Through 30 days, target vessel revascularization occurred in one patient (600-mg group) and there were no deaths. In this study, high-dose clopidogrel was not associated with bleeding complications.

The Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) trial evaluated the comparative efficacy of two different loading doses of clopidogrel (300-mg and 600-mg) alone and in combination with the glycoprotein (GP) IIb/IIIa inhibitor eptifibatide to address the limitations observed with the 300-mg loading dose of clopidogrel.[24] Clopidogrel was administered immediately after stenting. Results showed that the addition of eptifibatide to clopidogrel 600-mg produced a ≥2-fold increase in platelet inhibition at 3, 8, and 18–24 hours following stenting compared with clopidogrel 600-mg alone ($p < 0.001$), as measured by 5 μmol/L of ADP-induced aggregation. Treatment with 600 mg of clopidogrel produced better platelet inhibition than 300 mg of clopidogrel at all time points ($p < 0.001$). Maximum platelet inhibition induced by 600 mg of clopidogrel alone was observed at 8 hours after the procedure.

The more recent Clopidogrel optimal loading dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 study evaluated the efficacy and safety of higher versus standard dosages of clopidogrel and aspirin in more than 25,000 ACS patients with UA/NSTEMI (70.8%) and STEMI (29.2%).[14] These patients were managed with an early invasive strategy with intent for PCI as early as possible, but no later than 72 hours after randomization. This large factorial study compared high-dose clopidogrel (600-mg loading dose followed by 150 mg/day on days 2-7, then 75 mg/day) with the standard-dose regimen (300-mg loading dose followed by 75 mg/day) initiated as soon as possible and before PCI for preventing the composite of CV death, MI, or stroke at 30 days. The same composite endpoint was assessed in an evaluation of high-dose aspirin (300–325 mg/day) versus a lower daily dosage (75–100 mg/day). The safety of each regimen was evaluated as well.

Results of the CURRENT-OASIS 7 trial were presented at the 2009 European Society of Cardiology (ESC) Meeting.[25] Among the 25,000 ACS patients enrolled in this study, approximately 17,000 underwent PCI. A significant difference in outcomes was observed among patients who underwent PCI versus those who did not. In the overall population, the composite of CV death, MI, or stroke occurred in 4.2% of patients receiving high-dose clopidogrel therapy compared with 4.4% in the standard-dose group ($p = 0.370$). However, in patients who underwent PCI, a 15% reduction in the risk of CV death, MI, or stroke was observed in the high-dose clopidogrel group compared with patients receiving the standard-dose regimen ($p = 0.036$). A reduction in the rate of MI was also observed with high-dose clopidogrel (2.0%) compared with the standard-dose regimen (2.6%) in patients who underwent PCI ($p = 0.012$). Additionally, a 42% relative risk reduction in stent thrombosis was observed in patients receiving high-dose clopidogrel versus the standard-dose regimen ($p = 0.001$). For aspirin therapy, no difference in outcome was observed with the use of high-dose aspirin compared with the lower-dose regimen, and this outcome was not affected by the use of PCI.

High-dose clopidogrel was associated with an increase in major bleeding (Appendix A) compared with standard-dose clopidogrel in the overall study population (2.5% versus 2.0%; $p = 0.01$), as well as in those who underwent PCI (1.6% versus 1.1%; $p = 0.006$). An increase in severe bleeding was also observed in PCI patients receiving high-dose clopidogrel compared with those receiving the standard dose (1.1% versus 0.8%; $p = 0.034$). No increase in TIMI major bleeding, CABG-related bleeding, or fatal bleeding events was observed.[25]

Based on the findings from the CURRENT-OASIS 7 trial, use of high-dose clopidogrel for 7 days instead of the standard dose will prevent an additional 6 MIs and 7 stent thromboses, with an excess of 3 severe bleeds, for every 1,000 ACS patients undergoing PCI. For ACS patients not undergoing PCI, the standard-dose regimen of clopidogrel should be used.[25] In a press release issued by the ESC, Salim Yusuf, M.D., chair of the CURRENT-OASIS 7 steering committee, stated that the results from this study imply that the combination of high-dose clopidogrel and standard-dose aspirin may be the optimal treatment strategy for patients undergoing PCI.[26] The results of CURRENT-OASIS 7 were not available in time for inclusion in the 2009 ACC/AHA/SCAI STEMI/PCI joint guidelines.

Clopidogrel hyporesponsiveness

Despite the efficacy of clopidogrel in patients with ACS and in those undergoing PCI, this agent has been associated with significant limitations.[2] A considerable pretreatment period is necessary in patients receiving clopidogrel to achieve the desired antiplatelet effect. Steady-state levels of platelet aggregation are achieved 4–24 hours with a clopidogrel loading dose (300–600 mg) and within 4 to 7 days with a maintenance dosage of 75 mg/day.[27-29]

A modest antiplatelet effect has also been observed in laboratory testing of clopidogrel, and a considerable number of patients continue to experience CV events while taking this drug.[27,30] Use of multiple electrode platelet aggregometry to assess clopidogrel responsiveness demonstrated an association between low responsiveness to clopidogrel and stent thrombosis during the first 6 months after stent placement.[31] Ischemic events occurred early in the course after the procedure in the majority of low responders to clopidogrel with stent thrombosis.[31]

In vitro studies have demonstrated that responsiveness to clopidogrel is subject to interindividual and intraindividual variability, which may result in the occurrence of ischemic events after stent placement, stent thrombosis, and periprocedural MI.[30] The variable responsiveness with antiplatelet agents involves both pharmacokinetic and pharmacologic mechanisms,[32] and a combination of factors may influence the variability in response to clopidogrel (Appendix B). These factors include platelet function (i.e., increased sensitivity to collagen and ADP), genetic polymorphisms, reduced drug bioavailability (i.e., poor absorption, underdosing, patient noncompliance, interactions with other drugs), and the presence of diabetes, hypercholesterolemia, high body mass index, or smoking.[33] Steinhubl[34] stated that "every patient represents a unique and nonstatic combination of many influences (genetics, concomitant disease processes, medications, foods, age, and lifestyle), all of which culminate in variations not only in clopidogrel active metabolite formation but also in all aspects of measured on-treatment platelet function."

Gurbel et al.[27] evaluated the rate of clopidogrel resistance in patients undergoing elective coronary stenting before and at several timepoints following administration of standard-dose clopidogrel (300-mg loading dosage followed by a maintenance dosage of 75 mg/day). In this study, clopidogrel resistance was defined as the absolute difference between baseline aggregation and posttreatment aggregation (<10% reduction in aggregation in response to 5 μmol/L of ADP compared with pretreatment values). Using this definition, resistance was observed in 63% of patients at 2 hours, 31% at 24 hours, 31% at 5 days, and 15% at 30 days. Results showed that at 24 hours posttreatment, patients with the highest pretreatment platelet reactivity remained the most reactive ($p < 0.0001$). This was the first study to show that the platelet reactivity level following standard clopidogrel treatment for coronary stenting is crucially dependent on pretreatment reactivity. Further study is needed to investigate these findings and how they relate to the occurrence of ischemic events.[27]

Currently, there is no standard definition for clopidogrel hyporesponsiveness or resistance, and numerous additional terms have been used to define individuals who have ineffective platelet inhibition with clopidogrel, such as low-responder, semi-responder, and suboptimal responder.[30] Clopidogrel resistance has been defined as a <10% decrease in platelet resistance after the loading dose compared with baseline.[27,35] However, posttreatment platelet resistance, which does not require measurement of platelet resistance at baseline, has been shown to reflect thrombotic risk more reliably.[36]

The potentially severe consequences associated with variability in clopidogrel responsiveness, along with the confusion among health care professionals surrounding the limitations associated with clopidogrel, have led to a variety of questions. These questions include what should be considered the appropriate definition of clopidogrel resistance, should platelet function be routinely measured in ACS patients or those undergoing PCI and how should it be measured, and what measures should be undertaken when clopidogrel resistance is encountered?[37]

Overcoming the limitations of clopidogrel

Higher dosages of clopidogrel have been used in clinical practice, partly because of the desire for greater platelet aggregation inhibition. Low responders to clopidogrel may benefit from the use of a higher maintenance dosage of the drug. The Vasodilator-Stimulated Phosphoprotein-02 study investigated whether maintenance therapy with clopidogrel (150 mg/day) resulted in greater platelet inhibition than the standard dose (75 mg/day).[38] Results showed that the higher maintenance dosage produced a lower platelet reactivity index than the standard maintenance dosage after 2 weeks of therapy ($p < 0.0001$). In addition, the proportion of low responders was lower in patients receiving 150 mg/day of clopidogrel compared with those receiving 75 mg/day ($p = 0.0004$). However, these findings warrant further clinical evaluation, especially for long-term safety.

Prasugrel

Brandt et al.[39] observed that a 60-mg loading dose of prasugrel, a thienopyridine recently approved by FDA for the management of ACS patients undergoing PCI, produced relatively higher levels of active metabolite than observed with a 300-mg loading dose of clopidogrel, resulting in higher levels of mean platelet aggregation inhibition ($p < 0.01$) and lower interpatient variability ($p < 0.01$).

PRINCIPLE-TIMI 44. Prasugrel has been shown to be more potent than standard-dose clopidogrel in patients with coronary artery disease, but the relative antiplatelet effects of prasugrel versus high-dose clopidogrel were unknown. The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial,[40] a randomized, double-blind crossover study, compared prasugrel with high-dose clopidogrel in patients undergoing cardiac catheterization for planned PCI. In the loading-dose phase (prasugrel 60 mg; clopidogrel 600 mg), the primary endpoint was platelet aggregation inhibition with 20 μmol/L of ADP at 6 hours. Patients who underwent PCI entered the maintenance-dose phase, a 28-day crossover comparison of prasugrel (10 mg/day) and clopidogrel (150 mg/day). The primary endpoint of this phase was platelet aggregation inhibition with either drug at 14 days. Thienopyridine hyporesponsiveness was defined as platelet aggregation inhibition of < 20% with 20 μmol/L of ADP.

Results showed that among the 201 patients randomized in this study, platelet aggregation inhibition at 6 hours and during the maintenance phase was higher in patients who received prasugrel compared with those in the clopidogrel group ($p < 0.0001$, at both time points). Significant differences between the treatment groups were observed at 30 minutes and continued across all time points. The authors concluded that if achieving higher levels of platelet aggregation inhibition is a clinical goal, this can be accomplished more effectively with prasugrel than high-dose clopidogrel.[40]

TRITON-TIMI 38. The efficacy and safety of prasugrel and clopidogrel were compared in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38.[3] In this trial, 13,608 patients with moderate-to-high-risk ACS (UA/NSTEMI or STEMI) who were scheduled to undergo PCI were randomly assigned to receive prasugrel (60-mg loading dose followed by a 10 mg/day maintenance dosage) or clopidogrel (300-mg loading dose followed by a 75 mg/day maintenance dosage) for 6 to 15 months. The primary efficacy endpoint was a composite of death from CV causes, nonfatal MI, or nonfatal stroke, and the key safety endpoint was major bleeding (Appendix A).

In this trial, a 2.2% absolute reduction and a 19% relative reduction in the rate of the primary efficacy endpoint was observed with use of prasugrel compared with clopidogrel.[3] The primary efficacy endpoint occurred in 9.9% of patients receiving prasugrel and 12.1% of patients receiving clopidogrel ($p < 0.001$). Compared with clopidogrel, the rates of MI (9.7% versus 7.4%; $p < 0.001$), urgent target-vessel revascularization (3.7% versus 2.5%; $p < 0.001$), and stent thrombosis (2.4% versus 1.1%; $p < 0.001$) were decreased in patients receiving prasugrel.[3]

Major bleeding occurred in 2.4% of patients receiving prasugrel and 1.8% of patients receiving clopidogrel ($p = 0.03$). The rate of life-threatening bleeding was also higher in patients receiving prasugrel (1.4%) compared with those in the clopidogrel group (0.9%) ($p = 0.01$). There were no significant differences in overall mortality between the two treatment groups. The authors concluded that clinicians need to weigh the benefits and risks of intensive platelet aggregation inhibition when determining which antiplatelet regimen should be used in the treatment of ACS patients undergoing PCI.[3]

Landmark analyses of TRITON-TIMI 38[41] explored the effects of the loading and maintenance doses of prasugrel from randomization to day 3 and from day 3 to the end of the trial. A significant reduction in the primary efficacy endpoint was observed by the first prespecified time point (3 days), and continued throughout the follow-up period. A consistent pattern of significant reduction in the endpoints of MI, stent thrombosis, and urgent target vessel revascularization was observed during the first 3 days and from day 3 to the end of the trial. According to the authors, the superiority of both the loading and maintenance doses of prasugrel compared with standard-dose clopidogrel emphasizes the benefit of robust inhibition of platelet aggregation for the prevention of periprocedural and long-term ischemic events. However, compared with clopidogrel, prasugrel was associated with a significantly higher rate of major bleeding from day 3 until the end of the trial. Therefore, efforts are needed to minimize the risk of excess bleeding with prasugrel use.

Subgroup analyses. Occurrence of the primary endpoint (a composite of death from CV causes, nonfatal MI, or nonfatal stroke) has also been evaluated with the use of prasugrel versus clopidogrel in various patient subgroups from the TRITON-TIMI 38 trial. These include patients with diabetes, STEMI patients, and those who have undergone PCI and stenting.

Patients with diabetes and ACS are at high risk of recurrent CV events partly because of increased platelet activity. Multiple studies using various methods for measuring platelet function have shown reduced inhibition and higher rates of poor antiplatelet response to clopidogrel in patients with diabetes.[42-45] Wiviott and colleagues[46] evaluated the efficacy and safety of prasugrel versus clopidogrel among patients with and without diabetes mellitus in TRITON-TIMI 38, hypothesizing that a greater benefit would be observed with prasugrel. Analyses showed that the composite endpoint of death from CV causes, nonfatal MI, or nonfatal stroke occurred more frequently with clopidogrel (17%) compared with prasugrel (12.2%) in patients with diabetes ($p < 0.001$), as well as in those without diabetes (10.6% versus 9.2%, $p = 0.02$; $p_{interaction} = 0.09$).

Another subanalysis of TRITON-TIMI 38 assessed the occurrence and prevention of ischemic events in more than 12,500 patients who received at least one coronary stent and were treated with prasugrel or clopidogrel.[47] Compared with clopidogrel, the primary endpoint occurred less frequently with the use of prasugrel in the cohort that received at least one stent (11.9% versus 9.7%, $p = 0.0001$). The overall rate of stent thrombosis (definite or probable) was also reduced to a greater extent with the use of prasugrel (1.13%) compared with clopidogrel (2.35%) ($p < 0.0001$).

A TRITON-TIMI 38 subanalysis[48] also assessed the use of prasugrel versus clopidogrel in patients undergoing PCI for STEMI. The primary endpoint occurred in 6.5% of patients receiving prasugrel compared with 9.5% of individuals in the clopidogrel group ($p = 0.0017$). At 15 months, results showed that the primary endpoint occurred in 10% of prasugrel patients and 12.4% of clopidogrel patients ($p = 0.0221$).

Subanalysis of bleeding risk. In the subanalyses of patients with diabetes or STEMI and those undergoing PCI, there was no difference between the treatment groups in the occurrence of TIMI major bleeding unrelated to CABG at 30 days. The rate of bleeding was also evaluated in patients with previous stroke or transient ischemic attack (TIA), those 75 years of age or older, and patients with low body weight (<60 kg). Patients with these specific risk factors were further evaluated in TRITON-TIMI 38, with higher rates of bleeding observed in both clopidogrel-treated and prasugrel-treated patients who had at least one of these three risk factors compared to patients without them.[3] In patients with a history of cerebrovascular events, no evidence of a clinical benefit was observed from prasugrel compared with clopidogrel. There was significant harm with the use of prasugrel among patients with a history of cerebrovascular events, whereas a significant benefit with the use of prasugrel was observed among patients without such a history. In addition, a significant interaction between the presence or absence of any of these three risk factors and the degree of net clinical benefit for prasugrel compared with clopidogrel ($p = 0.006$) was observed, but no significant harm was evident. Results showed that among patients without any of these three risk factors, there was substantially favorable net clinical benefit for prasugrel use, greater efficacy with prasugrel ($p < 0.001$), and no significant difference in the rate of major bleeding in patients receiving prasugrel or clopidogrel ($p = 0.17$).

The findings from these evaluations led to a black box warning for bleeding risk in the labeling for prasugrel.[49] This black box warning states that the use of prasugrel is contraindicated in patients with a history of stroke or TIA. Because of the increased risk of fatal and intracranial bleeding and uncertain benefit, prasugrel use is generally not recommended in patients 75 years of age or older, except in high-risk patients (history of MI or diabetes), where the beneficial effect of this agent appears to be greater. Prasugrel should also be used with caution in patients weighing less than 60 kg due to increased bleeding risk. In these patients, a prasugrel maintenance dosage of 5 mg/day is recommended. A summary of the role of prasugrel versus clopidogrel in these patient subgroups is presented in Table 1.

TRILOGY ACS. The ongoing Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects with Unstable Angina/Non-ST Elevation Myocardial Infarction Who are Medically Managed (TRILOGY ACS) study is a Phase III, interventional, randomized, double-blind, active control, parallel assignment, safety and efficacy trial.[50] This trial is currently recruiting patients to evaluate the relative efficacy and safety of prasugrel (30-mg loading dose, followed by a 5-mg or 10-mg/day maintenance dosage) and clopidogrel (300-mg loading dose, 75 mg/day maintenance dosage) in ACS patients with UA/NSTEMI who are medically managed. All patients will receive aspirin therapy. The estimated date of trial completion is October 2011.

Ticagrelor

Ticagrelor, a new class of reversible P2Y12 inhibitor, is currently under investigation in clinical trials of ACS patients. This oral agent is not a prodrug and has a more rapid onset and more pronounced platelet inhibition than clopidogrel.[51,52] The Study of Platelet Inhibition and Patient Outcomes (PLATO)[5] was a multicenter, double-blind, randomized trial comparing ticagrelor (180-mg loading dose followed by 90 mg twice daily) with clopidogrel (300- or 600-mg loading dose followed by 75 mg/daily) for the prevention of CV events in approximately 18,500 ACS patients with or without ST-segment elevation. The primary endpoint was a composite of death from vascular causes, MI, or stroke, and the primary safety endpoint was total major bleeding (Appendix A).

Results of this trial showed that the primary endpoint occurred in 11.7% of patients receiving clopidogrel and 9.8% of patients in the ticagrelor group ($p < 0.001$). The rate of death from any cause was also lower in patients receiving ticagrelor (4.5%) compared with clopidogrel (5.9%) ($p < 0.001$). Significant differences were also observed with the rate of death from vascular causes (5.1% with clopidogrel and 4% with ticagrelor, $p = 0.001$) and MI alone (6.9% with clopidogrel and 5.8% with ticagrelor, $p = 0.005$), but not with stroke alone. The rate of definite stent thrombosis was lower in patients receiving ticagrelor (1.3%) compared with clopidogrel (1.9%) ($p = 0.009$).[5]

A prespecified subset analysis of ACS patients who were destined to undergo stenting ($n = 13,408$) prior to randomization to either study drug was also planned.[53] Results of this analysis showed that among ACS patients who underwent planned stenting, fewer CV events occurred

Table 1.
Preferred Thienopyridines for Acute Coronary Syndrome (ACS)[a]

ACS Situation	Preferred Thienopyridine
STEMI primary PCI	Prasugrel or clopidogrel
STEMI with fibrinolytics	Clopidogrel
NSTE ACS medical management	Clopidogrel
NSTE ACS PCI	Prasugrel or clopidogrel
Patient weight < 60 kg	Clopidogrel
Patient age ≥ 75 years	Clopidogrel
Patients with history of TIA or stroke	Clopidogrel
Patients with diabetes mellitus	Prasugrel

[a]Adapted from reference 50, with permission. STEMI = ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, NSTE = non-ST-segment elevation, TIA = transient ischemic attack.

in patients receiving ticagrelor compared with those who received clopidogrel. In addition, for every 1,000 patients admitted to the hospital for a planned invasive strategy, the use of ticagrelor instead of clopidogrel resulted in 11 fewer deaths, 13 fewer MIs, and 6 fewer cases of stent thrombosis at 12 months. Findings observed with the use of ticagrelor in this study were similar to those seen with prasugrel in terms of incremental reduction in the risk of coronary thrombotic events (e.g., MI) through more intense P2Y12 inhibition.[3]

In patients undergoing CABG, it is recommended that ticagrelor be withheld for 24 to 72 hours prior to surgery.[5] Since ticagrelor is a reversible P2Y12 inhibitor, the antiplatelet effect of this agent dissipates more rapidly than with thienopyridines, which are irreversible inhibitors. Therefore, less procedure-related bleeding may be expected with the use of ticagrelor. Results showed that there was no significant difference in the rate of bleeding between the two treatment groups in the PLATO trial (Appendix A). The more intense platelet inhibition with ticagrelor was not associated with an increased rate of any major bleeding. However, a higher rate of non–CABG-related bleeding was observed in patients receiving ticagrelor (4.5%) compared with those in the clopidogrel group (3.8%) ($p = 0.03$). Dyspnea occurred more frequently with ticagrelor compared with clopidogrel[5]; therefore, it has been suggested that patients with known breathing difficulties are not good candidates for ticagrelor.[54] The frequency of bradycardia was also higher in patients treated with ticagrelor despite the study exclusion criteria of patients with "increased risk of bradycardic events."[55] A new drug application for ticagrelor was submitted to FDA in November 2009.[56]

Other antiplatelet agents in clinical development

Clinical trials are ongoing to evaluate the efficacy and safety of thrombin-receptor antagonists (TRAs) in patients with atherosclerosis and ACS. Thrombin-receptor antagonists block the platelet protease-activated receptor (PAR)1, preventing thrombin-induced activation of platelets and arterial thrombus formation without affecting coagulation, bleeding time, or thrombin-mediated conversion of fibrinogen to fibrin.[57] SCH 530348 and E5555 are two TRAs in clinical development.[58] In the Phase II dose-ranging Thrombin Receptor Antagonist-Percutaneous Coronary Intervention (TRA-PCI) trial of patients undergoing nonurgent PCI, treatment with SCH 530348 added to clopidogrel and aspirin showed a similar rate of ischemic events (6% versus 9%) with no increased bleeding, which was the primary study end point.[59] In another Phase II trial performed in Japan, a significant reduction in the rate of periprocedural MI was observed in patients undergoing urgent PCI who received SCH 530348 plus standard treatment (i.e., aspirin, heparin, and ticlodipine) compared with standard treatment alone (16.9% versus 42.9%, respectively; $p = 0.013$). No excessive bleeding was seen in patients receiving SCH 530348 plus standard treatment.[60] SCH 530348 was granted fast-track status by FDA.[61] Phase III trials with SCH 530348 are ongoing.[62,63] E5555 is another PAR1 antagonist under clinical development in patients with coronary artery disease and ACS.[64,65] One study examined the in vitro effects of E5555 on platelet function beyond PAR1 blockade in healthy volunteers and patients with coronary artery disease who received aspirin with or without clopidogrel.[65] Moderate but significant inhibition of platelet activity beyond the PAR1 blockade was seen in vitro with E5555. The results suggest that this agent may enhance the antiplatelet potency of aspirin alone and combination therapy with aspirin and clopidogrel, providing rationale for the synergistic use of these agents.[65] Results for clinical end points from two completed Phase II trials have not been reported to date.[66,67]

Summary

Over the past decade, significant advances have been made with the use of oral antiplatelet agents in ACS patients and in those undergoing PCI and stenting. Dual antiplatelet therapy with clopidogrel and aspirin has been the standard of therapy in these patients. However, clopidogrel is associated with several limitations that can affect its efficacy. These limitations led to the investigation of newer, more potent oral antiplatelet agents, such as prasugrel and ticagrelor, but the increased antiplatelet effect of these agents may also be associated with an increased risk of bleeding. When determining the best antiplatelet therapy to use in patients with ACS or in those who have undergone PCI, health-system pharmacists must base treatment decisions on current practice guidelines, as well as individualized patient risk and benefit analyses.

Conclusion

Knowledge of the benefits and bleeding risks associated with oral antiplatelet agents, as well as guideline recommendations, can help health care providers make informed decisions regarding appropriate therapy for patients after ACS and PCI.

References

1. Rossini R, Musumeci G, Nijaradze T et al. Clopidogrel bisulfate: a review of its use in the management of acute coronary syndrome. *Clin Med Ther*. 2009; 1:899-910.
2. Schomig A. Ticagrelor—is there need for a new player in the antiplatelet-therapy field? *N Engl J Med*. 2009; 361:1108-11.
3. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357:2001-15.
4. Food and Drug Administration. FDA approves Effient to reduce the risk of heart attack in angioplasty patients. www.fda.gov/NewsEvents/Newsroom/

PressAnnouncements/ucm171497.htm (accessed 2010 Jan 8).
5. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009; 361:1045-57.
6. Lopes RD, Alexander JH, Granger CB et al. Antiplatelet therapy in patients with ACS—what is the role of new agents? www.theheart.org/article/1024921.do (accessed 2010 Jan 4).
7. Kushner FG, Hand M, Smith SC Jr et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009; 54:2205-41.
8. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007; 50:e1-157.
9. King SB III, Smith SC Jr, Hirshfeld JW Jr et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2008; 51:172-209.
10. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001; 345:494-502.
11. Antman EM, Morrow DA, McCabe CH et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J*. 2005; 149:217-26.
12. Stone GW, McLaurin BT, Cox DA et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006; 355:2203-16.
13. Subherwal S, Bach RG, Chen AY et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009; 119:1873-82.
14. Mehta SR, Bassand JP, Chrolavicius S et al. Design and rationale of CURRENT-OASIS 7: a randomized, 2 x 2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST-elevation acute coronary syndromes managed with an early invasive strategy. *Am Heart J*. 2008; 156:1080-8.
15. Rao SV, O'Grady K, Pieper KS et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol*. 2006; 47:809-16.
16. Stone GW, Witzenbichler B, Guagliumi G et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008; 358:2218-30.
17. Yusuf S, Mehta SR, Chrolavicius S et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006; 295:1519-30.
18. Yusuf S, Mehta SR, Chrolavicius S et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006; 354:1464-76.
19. Mehta SR, Yusuf S, Peters RJ et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001; 358:527-33.
20. Steinhubl SR, Berger PB, Mann JT III et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002; 288:2411-20.
21. Muller I, Seyfarth M, Rudiger S et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart*. 2001; 85:92-3.
22. Pache J, Kastrati A, Mehilli J et al. Clopidogrel therapy in patients undergoing coronary stenting: value of a high-loading-dose regimen. *Catheter Cardiovasc Interv*. 2002; 55:436-41.
23. Patti G, Colonna G, Pasceri V et al. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005; 111:2099-106.
24. Gurbel PA, Bliden KP, Zaman KA et al. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation*. 2005; 111:1153-9.
25. Mehta SR. A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes: results of the CURRENT OASIS 7 trial. Presented at the European Society of Cardiology Congress 2009. Barcelona, Spain; 2009 Aug 30. ESC 2009, presentation 177.
26. European Society of Cardiology. Double doses of clopidogrel better than standard doses for heart patients undergoing angioplasty, an international study finds. www.escardio.org/about/press/press-releases/esc09-barcelona/Pages/esc-2009-Mehta-Current%20Oasis%207.aspx (accessed 2010 Jan 11).
27. Gurbel PA, Bliden KP, Hiatt BL et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003; 107:2908-13.
28. Muller I, Besta F, Schulz C et al. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost*. 2003; 89:783-7.
29. Patrono C, Bachmann F, Baigent C et al. Expert consensus document on the use of antiplatelet agents. The Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. *Eur Heart J*. 2004; 25:166-81.
30. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol*. 2007; 49:1505-16.
31. Sibbing D, Morath T, Braun S et al. Clopidogrel response status assessed with Multiplate point-of-care analysis and the incidence and timing of stent thrombosis over six months following coronary stenting. *Thromb Haemost*. 2010; 103:151-9.
32. Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation*. 2007; 115:2196-207.
33. Sweeny JM, Gorog DA, Fuster V. Antiplatelet drug 'resistance'. Part 1: mechanisms and clinical measurements. *Nat Rev Cardiol*. 2009; 6:273-82.
34. Steinhubl SR. Genotyping, clopidogrel metabolism, and the search for the therapeutic window of thienopyridines. *Circulation*. 2010; 121:481-3.
35. Gurbel PA, Bliden KP, Hayes KM et al. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol*. 2005; 45:1392-6.
36. Samara WM, Bliden KP, Tantry US et al. The difference between clopidogrel re-

sponsiveness and posttreatment platelet reactivity. *Thromb Res*. 2005; 115:89-94.
37. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. *Circulation*. 2004; 109:3064-7.
38. Aleil B, Jacquemin L, De Poli F et al. Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. *JACC Cardiovasc Interv*. 2008; 1:631-8.
39. Brandt JT, Payne CD, Wiviott SD et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007; 153:66.e9-16.
40. Wiviott SD, Trenk D, Frelinger AL et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007; 116:2923-32.
41. Antman EM, Wiviott SD, Murphy SA et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol*. 2008; 51:2028-33.
42. Angiolillo DJ, Shoemaker SB, Desai B et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation*. 2007; 115:708-16.
43. Angiolillo DJ, Bernardo E, Ramirez C et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol*. 2006; 48:298-304.
44. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes*. 2005; 54:2430-5.
45. Serebruany VL, Malinin AI, Pokov A et al. Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in diabetic patients: the PLavix Use for Treatment Of Diabetes (PLUTO-Diabetes) trial. *Am Heart J*. 2008; 155:93-7.
46. Wiviott SD, Braunwald E, Angiolillo DJ et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation*. 2008; 118:1626-36.
47. Wiviott SD, Braunwald E, McCabe CH et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008; 371:1353-63.
48. Montalescot G, Wiviott SD, Braunwald E et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009; 373:723-31.
49. Effient (prasugrel) tablets package insert. Indianapolis, IN: Eli Lilly and Company; 2010 Jan 12.
50. ClinicalTrials.gov. A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects (TRILOGY ACS). www.clinicaltrials.gov/ct2/show/NCT00699998 (accessed 2010 Jan 11).
51. Storey RF, Husted S, Harrington RA et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007; 50:1852-6.
52. Husted S, Emanuelsson H, Heptinstall S et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006; 27:1038-47.
53. Cannon CP, Harrington RA, James S et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010; 375:283-93.
54. Peck P. TCT: PLATO subset analysis confirms tricagelor superiority. www.medpagetoday.com/MeetingCoverage/TCT/16136 (accessed 2010 Jan 12).
55. James S, Akerblom A, Cannon CP et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009; 157:599-605.
56. AstraZeneca. AstraZeneca submits US new drug application for Brilinta (ticagrelor), an investigational antiplatelet agent. www.astrazeneca.com/media/latest-press-releases/2009/Brilinta_NDA?itemId=7501665 (accessed 2010 Jan 8).
57. Angiolillo DJ, Capodanno D, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J*. 2010; 31:17-28.
58. Macaulay TE, Allen C, Ziada KM. Thrombin receptor antagonism—the potential of antiplatelet medication SCH 530348. *Expert Opin Pharmacother*. 2010; 11:1015-22.
59. Becker RC, Moliterno DJ, Jennings LK et al. Safety and tolerability of SCH 530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study. *Lancet*. 2009; 373:919-28.
60. Goto S, Yamaguchi T, Ikeda Y et al. Safety and exploratory efficacy of the novel thrombin receptor (PAR-1) antagonist SCH530348 for non-ST-segment elevation acute coronary syndrome. *J Atheroscler Thromb*. 2010; 17:156-64.
61. Hughes S. Major phase 3 program planned for new antiplatelet drug. www.theheart.org/article/786391.do (accessed 2010 May 26).
62. Morrow DA, Scirica BM, Fox KA et al. Evaluation of a novel antiplatelet agent for secondary prevention in patients with a history of atherosclerotic disease: design and rationale for the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2 degrees P)-TIMI 50 trial. *Am Heart J*. 2009; 158:335-41.
63. TRA*CER Executive and Steering Committees. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) trial: study design and rationale. *Am Heart J*. 2009; 158:327-34.
64. ClinicalTrials.gov. Safety and tolerability of E5555 and its effects on markers of intravascular inflammation in subjects with acute coronary syndrome. www.clinicaltrials.gov/ct2/show/NCT00548587 (accessed 2010 May 26).
65. Serebruany VL, Kogushi M, Dastros-Pitei D et al. The in-vitro effects of E5555, a protease-activated receptor (PAR)-1 antagonist, on platelet biomarkers in healthy volunteers and patients with coronary artery disease. *Thromb Haemost*. 2009; 102:111-9.
66. ClinicalTrials.gov. A double-blind study of E5555 in Japanese patients with acute coronary syndrome. www.clinicaltrials.gov/ct2/show/NCT00619164 (accessed 2010 May 26).
67. ClinicalTrials.gov. A double-blind study of E5555 in Japanese subjects with coronary artery disease. www.clinicaltrials.gov/ct2/show/NCT00540670 (accessed 2010 May 26).

Appendix A—Bleeding definitions in clinical trials

PLATO[5]: Major life-threatening bleeding: fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, reduction in Hgb of 5 g/dL, need for RBC transfusion of ≥ 4 units; other major bleeding: bleeding leading to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or associated with a reduction in Hgb of 3 to < 5 g/dL or requiring 2 to 3 unit RBC transfusion

TIMI[11]: Major bleeding: intracranial hemorrhage, clinically overt bleeding, reduction in Hgb of > 5 g/dL; minor bleeding: clinically overt bleeding or reduction in Hgb of 3 to < 5 g/dL

Modified TIMI: Severe bleeding: fatal, intracranial hemorrhage, cardiac tamponade, or clinically significant hemorrhage with reduction in Hgb of > 5 g/dL; minor bleeding: clinically overt hemorrhage with reduction in Hgb of > 3 to ≤ 5 g/dL

ACUITY[12]: Major bleeding: intracranial hemorrhage, intraocular bleeding, bleeding at access site requiring intervention, ≥ 5 cm hematoma, reduction in Hgb of ≥ 4 g/dL without an overt bleeding source, reduction in Hgb of ≥ 3 g/dL with an overt bleeding source, reoperation for bleeding, or blood product transfusion

CRUSADE[13]: Major bleeding: intracranial hemorrhage, retroperitoneal bleed, hematocrit drop of ≥ 12% (baseline to nadir), any RBC transfusion when baseline hematocrit is ≥ 28% with a witnessed bleed or any RBC transfusion when baseline hematocrit is < 28%

CURRENT-OASIS 7[14]: Severe bleeding: fatal or leading to reduction in Hgb of ≥ 5 g/dL, significant hypotension with need for inotropes, surgery (other than vascular site repair), symptomatic intracranial hemorrhage, RBC transfusion of ≥ 4 units or equivalent whole blood; other major bleeding: significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring RBC transfusion of 2 or 3 units or equivalent whole blood

GUSTO[15]: Severe bleeding: intracranial hemorrhage or bleeding resulting in hemodynamic compromise that requires intervention; moderate bleeding: bleeding requiring blood transfusion that does not result in hemodynamic compromise

HORIZONS-AMI[16]: Major bleeding: intracranial hemorrhage, intraocular, bleeding at access site with a ≥ 5-cm hematoma requiring intervention, reduction in Hgb of ≥ 4 g/dL without an overt bleeding source, reoperation for bleeding, or blood transfusion

OASIS[17,18]: Major bleeding: fatal, intracranial hemorrhage, intraocular, retroperitoneal, or needing surgical intervention, ≥ 2 units of blood transfused, or reduction in Hgb of > 3 g/dL

Appendix B—Mechanisms for clopidogrel hyporesponsiveness[30,34]

Genetic factors

- Polymorphisms of CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2C9
- Polymorphisms of ABCB1
- Polymorphisms of P2Y12
- Polymorphisms of GPIIIa

Cellular factors

- Increased ADP exposure
- Accelerated platelet turnover
- Upregulation of the P2Y1 and P2Y12 pathways

Clinical factors

- Poor adherence
- Poor absorption
- Diabetes mellitus/insulin resistance
- Elevated body mass index
- Drug-drug interactions involving CYP3A4
- Drug-drug interactions involving P-gp (also called MDRP or ABCB1)
- Drug-drug interactions involving CYP2C19
- Drug-drug interactions involving CYP2C9

Considerations in patients receiving oral antiplatelet therapy after acute coronary syndrome and percutaneous coronary intervention

DAVID S. ROFFMAN

Purpose: Adverse events that can occur in patients with acute coronary syndrome (ACS) following percutaneous coronary intervention (PCI), and with the use of oral antiplatelet agents are discussed.

Summary: Disruption of the vascular endothelium routinely occurs during PCI and stent placement, resulting in vascular injury. This injury can increase the risk of intracoronary thrombosis and subsequent ACS after PCI. Appropriate antiplatelet therapy reduces the risk of intracoronary thrombosis after PCI; however, health care providers should be aware of the possible limitations associated with specific antiplatelet agents and how to tailor therapy to improve outcomes. Platelet response after a clopidogrel loading dose is highly variable, and platelet hyporesponsiveness to clopidogrel may result in a variety of ischemic complications. A number of methods are available for assessing the antiplatelet effects of clopidogrel. However, none of these tests has been standardized as a measurement for clopidogrel responsiveness. Several polymorphic CYP enzymes are involved in the activation of clopidogrel, and genetic polymorphisms may affect the activity of these enzymes. Genetic variants, particularly the presence of the *CYP2C19*2* allele, are associated with poor clinical outcomes after stent placement, along with increased ischemic events in clopidogrel-treated patients. Health care providers should also be aware that drug-drug interactions can occur in patients receiving clopidogrel and other CYP2C19 inhibitors.

Conclusion: Prevention and proper management of adverse events can help to optimize outcomes in patients with ACS who have undergone PCI with stent placement.

Index terms: Acute coronary syndrome; Angioplasty; Clopidogrel; Coronary thrombosis; Drug interactions; Pharmacogenetics; Platelet aggregation inhibitors; Stents; Toxicity

Am J Health-Syst Pharm. 2010; 67(Suppl 7):S18-24

Disruption of the vascular endothelium routinely occurs during percutaneous coronary intervention (PCI) and stent placement, resulting in vascular injury. The vascular injury results in a cascade of events, including platelet activation and aggregation, which increases the risk of intracoronary thrombosis and subsequent acute coronary syndrome (ACS) after PCI. Appropriate antiplatelet therapy reduces the risk of intracoronary thrombosis after PCI.

Health-system pharmacists should be aware of the adverse events that can occur in ACS patients after PCI, and should be knowledgeable about the best ways to prevent, detect, and manage these events.

Complications after PCI

Despite significant advances in oral antiplatelet therapy for patients with ACS, thrombotic events continue to be a significant cause of morbidity and mortality after PCI and stent placement, both acutely and long term. Major complications after PCI include restenosis and stent thrombosis.[1] The frequent occurrence of restenosis with the use of bare-metal stents led to the use of drug-eluting stents (DES), which clearly reduces the rate of restenosis.[2]

Restenosis. A recent study evaluating the occurrence of restenosis fol-

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Based on the proceedings of a symposium held December 7, 2009, in conjunction with the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company.

Dr. Roffman reports that he has no relevant financial relationship with a commercial interest, as defined by the Accreditation Council for Pharmacy Education. He received an honorarium from Potomac Center for Medical Education (PCME) for his participation in the symposium and for his work on this article. This article was developed with the assistance of a medical writer working with PCME. Dr. Roffman approved the final article and all of its content.

DOI 10.2146/ajhp100166

lowing DES placement demonstrated a restenosis rate of 3.5% per stent after 1 year and 4.9% after 2 years.[3] A higher risk of restenosis was observed in patients with diabetes mellitus compared with those without diabetes, and this risk differed with the type of DES used. Compared with other types of DES, restenosis was twice as frequent with the zotarolimus-eluting stent in patients with diabetes; higher restenosis rates were also observed with the sirolimus-eluting stent. However, the rate of restenosis with use of paclitaxel-eluting stents was unrelated to diabetes mellitus.[3]

Stent thrombosis. Stent thrombosis has traditionally been thought to occur during the first 30 days after PCI. However, risk of this complication may extend beyond this time due to delayed endothelialization associated with DES implantation. Iakovou et al.[4] conducted a study to evaluate the rate and clinical outcomes of stent thrombosis following routine implantation of paclitaxel-eluting or sirolimus-eluting stents. Nine months after implantation, stent thrombosis had occurred in 1.3% of patients ($p = 0.09$), with subacute thrombosis (≤ 30 days) observed in 0.6% and late thrombosis (> 30 days) occurring in 0.7% of patients. Among the subacute thrombosis cases, 71% occurred within 1 week after the procedure, while 53% of the late thrombosis cases occurred within 3 months after the procedure. Among the 29 cases of stent thrombosis, 2 (7%) presented as unstable angina, 20 (69%) presented as nonfatal myocardial infarction (MI), and 7 (24%) were fatal. It is believed that the cumulative rate of stent thrombosis following successful DES implantation in "real-world" patients is substantially higher than the rate reported in clinical trials.[4]

This study also identified premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and a low ejection fraction as primary independent predictors of in-stent thrombosis.[4] Stent length was also a predictor for subacute thrombosis, with a 1.03 times greater risk of thrombosis for each 1-mm increase in length. Among these risk factors for thrombosis, early discontinuation of antiplatelet therapy was associated with the highest rate (29%) of events. A large registry demonstrated that clopidogrel discontinuation following DES placement (3 months for a sirolimus-eluting stent; 6 months for a paclitaxel-eluting stent) was associated with a significant increase (approximately 70 times) in stent thrombosis.[4]

Patients must be educated on the importance of taking their antiplatelet medications and the risks associated with their discontinuation.

Metabolic pathways of antiplatelet agents

The thienopyridines prasugrel and clopidogrel are prodrugs that are activated through some similar and some differing metabolic pathways. Both agents are converted into active metabolites that selectively and irreversibly bind to the P2Y12 receptor on the platelet membrane for the lifespan of the platelet. Clopidogrel conversion is achieved through the hepatic cytochrome P450 (CYP) isoenzyme system in a two-step process that involves a variety of CYP isoenzymes, including CYP2C19 and CYP2B6.[5] This two-step process is susceptible to interference from genetic polymorphisms and drug-drug interactions.[6,7] Clopidogrel is also associated with a dose-dependent delayed onset of action and large inter-individual variability in platelet response.[5] Prasugrel is rapidly hydrolyzed via esterases to an intermediate metabolite.[1] Only one CYP-dependent oxidation step involving various CYP isoenzymes, including CYP2C19, is required for conversion to the active compound of prasugrel, compared to the two-step requirement for clopidogrel.[5] Compared with clopidogrel, a lower variability of platelet response and no measurable vulnerability to genetic variation in CYP isoenzymes has been observed with prasugrel.[8,9] However, the limitation of the irreversibility of the thienopyridine effect is more evident with prasugrel compared with clopidogrel.[5]

Response variability with clopidogrel

Platelet response after administration of a clopidogrel loading dose is highly variable. A database of patients ($n = 544$) from various studies was analyzed to determine individual response to clopidogrel.[10] Results revealed a normal distribution when residual platelet aggregation was induced by 5 μmol/L of adenosine diphosphate (ADP) after clopidogrel administration. When hyporesponsiveness and hyperresponsiveness to clopidogrel were considered to be two standard deviations less than and greater than the mean, respectively, there was similarity between the prevalence of hyporesponsiveness (4.8%) and hyperresponsiveness (4.2%) to clopidogrel. Several studies have demonstrated that genetic polymorphisms of the CYP2C19 isoenzyme, which produce a "loss of function" allele, increase the risk of intracoronary thrombotic events. Variability in individual responsiveness to clopidogrel and the implications of this variability have been the topics of intense discussion and study over the past few years.

Platelet hyporesponsiveness to clopidogrel may result in a variety of ischemic complications, including stent thrombosis and periprocedural MI.[11] It has been shown that excessive on-treatment platelet reactivity after clopidogrel administration is associated with an increased risk of adverse events following PCI with stent placement. Data from one trial showed a greater than six-fold increase in the risk of death, MI, and target vessel reintervention after stent placement at

30 days if 5 μmol/L of ADP-induced residual platelet aggregation (RPA) was >14% following a 600-mg loading dose of clopidogrel.[12]

Methods for assessing antiplatelet effects

It is important to identify patients who are not adequately protected by clopidogrel therapy. Several methods are available for assessing the antiplatelet effects of clopidogrel. However, none of these tests has been standardized as a measurement for clopidogrel responsiveness. Turbidometric light transmittance aggregometry (LTA) using ADP as an agonist is currently considered the gold standard technique for assessing clopidogrel response.[11] LTA measures the increase in light transmission as a result of platelet aggregation. Simply explained, a beam of light will not easily pass through platelet-rich plasma. However, following platelet aggregation due to the addition of an agonist such as ADP, more light passes through the plasma, providing information about platelet aggregation in vitro.[1] A variety of methodological variables associated with LTA (e.g., agonist dose, LTA value, nature of the anticoagulant) may result in variances in the prevalence of poor responders.[13,14] Additionally, LTA is time-consuming, technically demanding, and not widely available.[11]

Clopidogrel prevents ADP-induced platelet activation through inhibition of the P2Y12 receptor. However, other ADP receptor subtypes may still be activated and contribute to platelet aggregation during thienopyridine treatment.[15] This undermines the use of LTA to define clopidogrel-induced antiplatelet effects, and has led to the development of assays that are more specific to the P2Y12 pathway.[11] Assessment of vasodilator-stimulated phosphoprotein (VASP) phosphorylation using flow cytometry can also provide important information regarding responsiveness of clopidogrel, since VASP phosphorylation depends on the level of P2Y12 receptor activation.[16] Use of a flow cytometric assay is associated with several drawbacks, including expense and the need for experienced personnel.[17] This test is also time-consuming, with results of one study showing that the median time between administration of the first clopidogrel dose and performing the first VASP assay was 24 hours, and repeat testing is often necessary.[17,18]

Several point-of-care methods are available for assessing platelet function (e.g., PFA-100 [Dade Diagnostika, GmbH, Germany], Plateletworks [Helena Laboratories, Beaumont, TX], VerifyNow [Accumetrics, San Diego, CA]). Simple assays such as these are more practical in the clinical setting because of their wide availability and ease of use.[11,19] The Gauging Responsiveness with A VerifyNow Assay-Impact on Thrombosis And Safety (GRAVITAS) trial is being conducted to evaluate the use of a point-of-care assay for tailoring antiplatelet therapy with clopidogrel to reduce major adverse cardiovascular events following DES implantation.[20]

Reducing the rate of platelet resistance

Various studies have investigated ways to reduce the rate of platelet resistance in patients taking thienopyridines. Gurbel and colleagues[21] conducted a study to determine the effect of clopidogrel dosage (300-mg versus 600-mg loading dose) on the rate of hyporesponsiveness. Results showed that the rate of hyporesponsiveness was lower with the 600-mg loading dose (8%) compared with the 300-mg loading dose (28%) with 5 μmol/L of ADP and 8% and 32%, respectively, with 20 μmol/L of ADP ($p < 0.001$). The authors concluded that the 600-mg clopidogrel loading dose reduced the rate of hyporesponsiveness compared with a 300-mg loading dose.

Another study compared the rate of onset, magnitude, and consistency of platelet inhibition following administration of clopidogrel or prasugrel.[22] Patients received a loading dose of either clopidogrel (300 mg) or prasugrel (60 mg). Turbidometric aggregometry was used to measure platelet aggregation response to 5 and 20 μmol/L of ADP. A more rapid, potent, and consistent inhibition of platelet function was observed with prasugrel compared with clopidogrel. Results showed that inhibition of platelet aggregation (IPA) was higher with prasugrel compared with clopidogrel from 15 minutes through 24 hours with 5 μmol/L of ADP, as well as from 30 minutes through 24 hours with 20 μmol/L of ADP ($p < 0.01$). Response to prasugrel was more consistent than response to clopidogrel ($p < 0.01$). The lower IPA response to clopidogrel was associated with lower plasma concentrations of active metabolite ($p < 0.001$). In this study, patients who were resistant to clopidogrel (300 mg) remained sensitive to prasugrel (60 mg).

Genetic polymorphisms and response to antiplatelet therapy

Knowledge of the human genome and how it interacts with individual patient responsiveness to pharmacotherapy can be helpful in determining which patients may experience an inadequate response to clopidogrel. Several CYP isoenzymes are involved in the activation of clopidogrel, and the activity of these enzymes may be affected by genetic polymorphisms.[5] CYP2C19 is involved in the conversion from clopidogrel to its active metabolite and to the intermediate metabolite, 2-oxo-clopidogrel. The pharmacokinetics and antiplatelet effects of clopidogrel differ according to the *CYP2C19* genotype, as measured by ex vivo platelet aggregation assays, and particular *CYP2C19* alleles have been identified as being responsible for a loss of response in different ethnic populations. The *CYP2C19*1* allele relates to fully functional metabolic activation, while the *CYP2C19*2* and *CYP2C19*3* alleles are associated with reduced metabolic activation.[23]

The wild-type *CYP2C19*1/*1* allele, which is associated with a higher degree of extensive metabolic activation, has been found with greater frequency in white patients (74%) compared with African Americans (66%), and Asians (38%). When evaluating alleles that are associated with a loss of response to clopidogrel, the *CYP2C19*1/*2* or *CYP2C19*1/*3* allele, which is associated with intermediate metabolic activation, occurs more frequently in Asians (50%) than in blacks (29%) and whites (26%). The *CYP2C19*2/*2*, *CYP2C19*2/*3*, or *CYP2C19*3/*3* allele, which is associated with poor metabolic activation, occurs more frequently in Asians (14%) compared with black (4%) and white (2%) patients.[23]

Trenk and colleagues[24] examined the loss of function *CYP2C19*2* polymorphism and its association with high on-treatment platelet reactivity (>14% RPA) following clopidogrel administration. The effect of high on-treatment RPA on clinical outcomes after stent placement was also evaluated. Among 797 patients in this study, 69.3% were *CYP2C19* wild-type homozygotes (**1/*1*) and 30.7% carried at least one *CYP2C19*2* allele. No significant difference in RPA was observed between genotypes at baseline. However, after a clopidogrel loading dose, RPA was higher in *CYP2C19*2* carriers compared with wild-type homozygotes ($p < 0.001$). The rate of high on-treatment platelet reactivity was also higher in *CYP2C19*2* carriers ($p < 0.001$). At predischarge (after the first 75-mg clopidogrel maintenance dose), RPA >14% was associated with a 3-fold increase in the rates of death and MI at 1 year ($p = 0.004$). The authors concluded that high on-clopidogrel platelet reactivity is more likely to occur in patients carrying at least one *CYP2C19*2* allele, and this reactivity is associated with poor clinical outcomes following stent placement.

The Pharmacogenomics of Antiplatelet Intervention (PAPI) study evaluated the use of clopidogrel in the Amish population.[25] The first part of this study was undertaken to identify specific genes associated with a variation in response to clopidogrel, while the second part of the study examined the extension of the genetic findings and the time-to-event analysis in high-risk patients with cardiovascular disease. In this trial, 429 genetically homogeneous patients received a 300-mg loading dose of clopidogrel, followed by a 75 mg/day maintenance dosage for 6 days. LTA was used to measure platelet activity. Looking at ADP-stimulated (20 μmol/L) platelet aggregation, there was a clear shift toward less platelet aggregation after 7 days of clopidogrel administration compared with before clopidogrel was administered. However, a wide variability in platelet aggregation was observed and there was no clear cutoff to define platelet resistance in this population.

In the PAPI study, a number of clinical factors that correlated very well with poor platelet responsiveness were observed, such as increased age, decreased weight, and increased triglyceride levels.[25] It was determined that these clinical predictors of poor responsiveness accounted for approximately 10% of the variation in response to clopidogrel. Looking at a genetic component for clopidogrel response variation, it was found that most of the study participants had the wild-type allele, which does not contribute to loss of function, and the intermediate allele was observed in approximately one third of patients. Approximately 10% of patients were homozygous for the *CYP2C19*2* allele, which is associated with poor metabolism. Patients with this genetic variant were more likely than patients without the *CYP2C19*2* allele to experience a cardiovascular event or death during 1 year of follow-up (20.9% versus 10.0%, respectively; $p = 0.02$).

Based on the results of this study, the authors concluded that genetics account for approximately 12% of the variation in response to clopidogrel, while another 10% is due to clinical factors.[25] Based on these findings, approximately 75% of the factors that contribute to a variable response to clopidogrel still need to be determined.[1]

Genetic variability in clopidogrel-treated patients. Another study evaluated the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel therapy in 162 patients.[7] The results of this study showed that approximately 30% of participants were a carrier of at least one *CYP2C19* reduced-function allele. Compared with noncarriers, these patients had a 32.4% relative reduction in plasma exposure to the active metabolite of clopidogrel ($p < 0.001$). A 9% absolute reduction in maximal platelet aggregation in response to clopidogrel therapy was observed in carriers compared with noncarriers ($p < 0.001$). This study also examined the association between genetic variants and cardiovascular outcomes in 1477 ACS patients who received clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38. A relative increase of 53% was observed in the composite primary efficacy outcome (risk of death from cardiovascular causes, MI, or stroke) among carriers versus noncarriers ($p = 0.01$). An increase in the risk of stent thrombosis was also observed in carriers (2.6%) compared with noncarriers (0.8%) ($p = 0.02$). The authors concluded that the results of this study showed that genetic variation has an effect on clinical and pharmacologic responses to clopidogrel.

Genetic variability in prasugrel-treated patients. Mega et al.[8] evaluated the association between functional variants in CYP genes, plasma concentrations of active drug metabolites, and platelet inhibition in response to prasugrel in 238 patients. Results showed no significant decrease in the pharmacokinetic or pharmacodynamic response to prasugrel among carriers of at least one reduced-function allele (e.g., *CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP3A5*, and *CYP1A2*) compared with noncarriers. This study then examined the association of these genetic variants with cardiovascular outcomes in a cohort of 1466 ACS patients allocated to receive prasugrel in TRITON-TIMI 38. No significant associations were found between any of the tested CYP genotypes and risk of cardiovascular death, MI, or stroke in ACS patients treated with prasugrel. The authors concluded that no CYP genetic variants were found that affected active drug metabolite levels and platelet inhibition in patients who received prasugrel. Additionally, no CYP variants affected cardiovascular outcomes in ACS patients receiving prasugrel who underwent PCI. These genetic observations explain some of the differences in the clinical and pharmacologic response to treatment using prasugrel compared with clopidogrel, and may be useful for individualizing pharmacotherapy in the future.

Drug-drug interactions with CYP2C19 inhibitors

There are various CYP2C19 inhibitors that may attenuate the antiplatelet effects of clopidogrel. These include the proton pump inhibitors (PPIs) omeprazole and esomeprazole, the histamine H_2-receptor antagonist cimetidine, and the selective serotonin reuptake inhibitor fluoxetine.[25]

PPIs and clopidogrel. The 2008 Expert Consensus Document on Reducing the Gastrointestinal Risk of Antiplatelet Therapy and NSAID Use recommended that patients on dual antiplatelet therapy receive PPI prophylaxis to decrease the risk of adverse gastrointestinal bleeding.[26]

The isoenzyme CYP2C19 is involved in the metabolism of PPIs, and multiple studies have shown that use of clopidogrel with PPIs, increases the risk of adverse events.[6,27-29] Investigators in the Omeprazole Clopidogrel Aspirin (OCLA) study hypothesized that PPIs reduce the biologic action of clopidogrel.[6] Patients undergoing stent implantation received clopidogrel (a 300-mg loading dose followed by 75 mg/day) and aspirin (75 mg/day), and then were randomized to receive omeprazole (20 mg/day) or placebo. VASP phosphorylation analysis was performed on days 1 and 7 to measure platelet reactivity in approximately 125 patients. A decrease in the platelet reactivity index was observed on day 7 in patients receiving omeprazole (39.8%) compared with that in patients receiving placebo (51.4%) ($p < 0.0001$).

A retrospective cohort study of more than 8000 ACS patients evaluated outcomes in patients taking clopidogrel with or without a PPI following hospitalization.[27] The main outcome measure was all-cause mortality or hospitalization for ACS. Results showed that 63.9% of patients were prescribed a PPI at discharge, during follow-up, or both, while 36.1% of patients were not prescribed a PPI. Use of clopidogrel with a PPI was associated with an increased risk of death or rehospitalization for ACS compared with the use of clopidogrel alone (adjusted odds ratio, 1.25; 95% confidence interval, 1.11–1.41), while clopidogrel without a PPI was associated with the lowest event rate. The authors concluded that the results of this study suggest that PPIs should be used in patients receiving clopidogrel who have a clear indication for PPI use and not for routine prophylaxis.

Post-hoc analysis of the TRITON-TIMI 38 and The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial used a multivariate Cox model with propensity score to assess the association of PPI use with risk of clinical outcomes.[28] In the PRINCIPLE-TIMI 44 trial, mean platelet aggregation was lower following a 600-mg loading dose of clopidogrel in patients receiving a PPI compared with those not receiving PPI therapy ($p = 0.02$). However, in patients receiving a 60-mg loading dose of prasugrel, a more modest difference was observed in mean platelet aggregation with or without a PPI ($p = 0.054$). In TRITON-TIMI 38, 33% of patients were receiving PPI therapy at randomization. No association between PPI use and the risk of cardiovascular death, MI, or stroke was observed in patients receiving either clopidogrel or prasugrel. According to the authors, the findings of this analysis do not support the need to avoid concomitant use of clopidogrel or prasugrel and PPIs when the agents are clinically indicated.

The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial, a multicenter, international, double-blind, double-dummy, placebo-controlled, parallel group, Phase III efficacy and safety study, was the first prospective randomized clinical trial to compare omeprazole with placebo in patients receiving clopidogrel.[29] This trial was conducted to determine whether PPI therapy reduced important gastrointestinal (GI) events (e.g., upper GI bleeding, symptomatic upper GI bleeding, and pain of presumed GI origin with underlying multiple erosive disease) compared with placebo in patients on dual antiplatelet therapy (clopidogrel and aspirin). A secondary outcome measure of the trial was the occurrence of a cardiovascular event in patients receiving clopidogrel and PPI therapy. The cardiovascular endpoint was a composite of cardiovascular death, nonfatal MI, ischemic stroke, or PCI or coronary artery bypass grafting.[29]

The COGENT trial compared the use of GCT-2168, a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg), with clopidogrel alone in patients requiring antiplatelet therapy with clopidogrel for at least 12 months, typically after non-ST segment elevation ACS, ST-segment elevation MI, or stent implantation. Patients were stratified at baseline based on *Helicobacter pylori* serology (positive or negative) and concomitant use of any type of nonsteroidal anti-inflammatory drug (NSAID). This study enrolled approximately 3600 patients and was stopped early when the sponsor declared bankruptcy.[29]

Results from the COGENT trial were presented at the 2009 Transcatheter Cardiovascular Therapeutics (TCT) meeting. Preliminary analysis showed that the addition of a PPI to clopidogrel reduced the risk of GI events by 45% compared with the use of clopidogrel alone ($p = 0.007$).[29] The data from this trial also indicate that there is no clinically relevant adverse cardiovascular interaction between clopidogrel and PPIs, as the number of cardiovascular events was similar between the treatment (69 events) and placebo (67 events) groups.

Despite the findings from the COGENT trial, the Food and Drug Administration (FDA) issued a new public health warning regarding concomitant use of clopidogrel and omeprazole less than 2 months after the TCT meeting.[30] Issued on November 17, 2009, this warning stated the following:

> New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole.

Clopidogrel labeling was also updated to include information regarding the drug-drug interaction between clopidogrel and omeprazole.[23] The announcement from FDA was not anticipated by many health care professionals, especially since it came following presentation of the results from COGENT. Additional studies regarding the clopidogrel-PPI interaction are ongoing.[31]

Summary

Patients with ACS may experience a variety of adverse intracoronary thrombotic events. In-stent thrombosis is a significant complication after PCI. Independent predictors of stent thrombosis have been identified, with nonadherence to thienopyridine therapy considered a significant contributor to DES thrombosis. Hyporesponsiveness to clopidogrel therapy may also lead to ischemic events, and it is important to identify patients who are not adequately protected by clopidogrel therapy. A number of methods are available for assessing the antiplatelet effects of clopidogrel. However, none of these tests has been standardized as a measurement for clopidogrel responsiveness. Although good results have been observed with the use of point of care methods, further evaluation is needed before determining the clinical utility of platelet function testing.

Several polymorphic CYP enzymes are involved in the activation of clopidogrel, and the activity of these enzymes may be affected by genetic polymorphisms. Genetic variants, particularly the presence of the *CYP2C19*2* allele, are associated with poor clinical outcomes following stent placement, along with increased ischemic events in clopidogrel-treated patients. In patients treated with prasugrel, the *CYP2C19*2* allele does not appear to affect active drug metabolite levels, platelet inhibition, or cardiovascular outcomes. These findings may be useful for individualizing pharmacotherapy in the future.

Drug-drug interactions can occur in patients receiving clopidogrel and other CYP2C19 inhibitors. An increased risk of thrombotic events has been observed in some evaluations of the concomitant use of clopidogrel and omeprazole and, to a lesser extent, some other PPIs, while other studies, including a large, prospective, randomized, clinical trial, have shown no increased risk of adverse events. FDA has issued a public health warning regarding concomitant use of clopidogrel and omeprazole.

It is important for health-system pharmacists to be knowledgeable about the adverse events that can occur in the treatment of ACS, the reasons for their occurrence, and the best options for preventing and managing these events.

Conclusion

Prevention and proper management of adverse events can help to optimize outcomes in patients with ACS who have undergone PCI with stent placement.

References

1. Malenka DJ, Kaplan AV, Lucas FL et al. Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. *JAMA*. 2008; 299:2868-76.
2. James SK, Stenestrand U, Lindback J et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. *N Engl J Med*. 2009; 360:1933-45.
3. Frobert O, Lagerqvist B, Carlsson J et al. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). *J Am Coll Cardiol*. 2009; 53:1660-7.
4. Iakovou I, Schmidt T, Bonizzoni E et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005; 293:2126-30.
5. Schomig A. Ticagrelor—is there need for a new player in the antiplatelet-therapy field? *N Engl J Med*. 2009; 361:1108-11.
6. Gilard M, Arnaud B, Cornily JC et al. In-

fluence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008; 51:256-60.
7. Mega JL, Close SL, Wiviott SD et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009; 360:354-62.
8. Mega JL, Close SL, Wiviott SD et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009; 119:2553-60.
9. Wiviott SD, Trenk D, Frelinger AL et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007; 116:2923-32.
10. Serebruany VL, Steinhubl SR, Berger PB et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol*. 2005; 45:246-51.
11. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol*. 2007; 49:1505-16.
12. Hochholzer W, Trenk D, Bestehorn HP et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol*. 2006; 48:1742-50.
13. Frelinger AL III, Michelson AD. Clopidogrel linking evaluation of platelet response variability to mechanism of action. *J Am Coll Cardiol*. 2005; 46:646-7.
14. Labarthe B, Theroux P, Angioi M et al. Matching the evaluation of the clinical efficacy of clopidogrel to platelet function tests relevant to the biological properties of the drug. *J Am Coll Cardiol*. 2005; 46:638-45.
15. Storey RF, Newby LJ, Heptinstall S. Effects of P2Y(1) and P2Y(12) receptor antagonists on platelet aggregation induced by different agonists in human whole blood. *Platelets*. 2001; 12:443-7.
16. Aleil B, Ravanat C, Cazenave JP et al. Flow cytometric analysis of intraplatelet VASP phosphorylation for the detection of clopidogrel resistance in patients with ischemic cardiovascular diseases. *J Thromb Haemost*. 2005; 3:85-92.
17. Kleiman NS. Will measuring vasodilator-stimulated phosphoprotein phosphorylation help us optimize the loading dose of clopidogrel? *J Am Coll Cardiol*. 2008; 51:1412-4.
18. Bonello L, Camoin-Jau L, Arques S et al. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol*. 2008; 51:1404-11.
19. Accumetrics. VerifyNow P2Y12 test. www.accumetrics.com/products/vnp2y12.aspx (accessed 2010 Feb 5).
20. ClinicalTrials.gov. GRAVITAS: Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety. www.clinicaltrials.gov/ct2/show/NCT00645918 (accessed 2010 Feb 4).
21. Gurbel PA, Bliden KP, Hayes KM et al. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol*. 2005; 45:1392-6.
22. Brandt JT, Payne CD, Wiviott SD et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007; 153:66.e9-16.
23. Plavix (clopidogrel bisulfate) tablets package insert. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2010 Mar.
24. Trenk D, Hochholzer W, Fromm MF et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol*. 2008; 51:1925-34.
25. Shuldiner AR, O'Connell JR, Bliden KP et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009; 302:849-57.
26. Bhatt DL, Scheiman J, Abraham NS et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2008; 118:1894-909.
27. Ho PM, Maddox TM, Wang L et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009; 301:937-44.
28. O'Donoghue ML, Braunwald E, Antman EM et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet*. 2009; 374:989-97.
29. Bhatt DL. The COGENT trial. Late-breaking clinical trials II. Paper presented at Transcatheter Cardiovascular Therapeutics Meeting. San Francisco, CA; 2009 Sept 24.
30. Food and Drug Administration. Information for healthcare professionals: update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as prilosec and prilosec OTC). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm (accessed 2010 Feb 6).
31. Hughes S. Cardiologists shocked by new FDA alert on clopidogrel-PPI interaction. www.theheart.org/article/1025121.do (accessed 2010 Feb 6).

Case report: A 55-year-old woman with chest pain upon arrival to the emergency department

SANDEEP NATHAN

Purpose: The case of a woman with progressive substernal chest pain is described.

Summary: A 55-year-old woman arrived at the emergency department (ED) with a complaint of progressive substernal chest pain. Her medical history included hypertension and dyslipidemia. Upon arrival to the ED, the patient was free of chest pain. A chest x-ray was essentially unremarkable, and nonspecific inferolateral electrical changes were observed on the initial electrocardiogram (ECG). Initial laboratory test results were unremarkable, with the exception of the cardiac troponin level (0.23 µg/L). However, the patient complained of recurrent chest pain, and an immediate repeat ECG showed fairly significant new ST-segment depression. The patient was diagnosed with non-ST-elevation acute coronary syndrome (ACS). She received 600 mg of clopidogrel, along with i.v nitroglycerin, and subsequently underwent cardiac catheterization. Orthogonal views of the left coronary system clearly showed a high-grade lesion in the middle of the left anterior descending (LAD) artery. Percutaneous coronary intervention (PCI) was performed on the mid-LAD lesion using bivalirudin for procedural anticoagulation, and a 3.0 x 18 mm drug-eluting stent was implanted in the mid-LAD vessel. Brisk blood flow to the distal territory was observed at the conclusion of the case. The patient remained asymptomatic after PCI and was discharged on day 3 on several medications.

Conclusion: Discussion of a patient with non-ST elevation ACS illustrates some of the clinical issues surrounding PCI and stent implantation, including selection and use of antiplatelet therapy.

Index terms: Acute coronary syndrome; Angioplasty; Anticoagulants; Bivalirudin; Cardiac drugs; Clopidogrel; Diagnosis; Drugs; Electrocardiography; Nitroglycerin; Platelet aggregation inhibitors; Stents

Am J Health-Syst Pharm. 2010; 67(Suppl 7):S25-7

This case report discusses the presentation and management of an actual patient. Key pieces of identifying information have been changed, but the case itself has not been embellished in any way. This case illustrates some of the main clinical issues surrounding the selection and use of antiplatelet therapy in acute coronary syndrome (ACS).

Case report

A 55-year-old woman arrived at the emergency department (ED) with a complaint of progressive substernal chest pain over the past 3 days. She stated that the pain began intermittently following an unusually vigorous workout. She initially believed that her pain was due to a musculoskeletal issue, which she treated with acetaminophen and nonsteroidal antiinflammatory drugs; she did not experience any relief. The patient became concerned when the pain began to worsen. She described the pain as dull and pressure-like with associated dyspnea and mild nausea. Before arriving at the ED, the pain was occurring at rest and each episode lasted up to 15 minutes.

The patient's medical history included hypertension and dyslipidemia. She was taking amlodipine (10 mg/day) and hydrochlorothiazide (25 mg/day) to manage her hypertension, and her dyslipidemia

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Based on the proceedings of a symposium held December 7, 2009, in conjunction with the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from Daiichi Sankyo, Inc. and Eli Lilly and Company.

Dr. Nathan has served on the speakers' bureaus for Sanofi Aventis, Medicure, Inc., Schering-Plough, and Medtronic and as a consultant and advisory panel member for Sanofi Aventis, Medicure, Inc., and Schering-Plough, and has provided research support to Medicure, Inc. He received an honorarium from Potomac Center for Medical Education (PCME) for his participation in the symposium and for his work on this article. This article was developed with the assistance of a medical writer working with PCME. Dr. Nathan approved the final article and all of its content.

DOI 10.2146/ajhp100167

was being controlled with diet. The patient had been postmenopausal for a number of years and had no known drug allergies. She reported drinking alcohol socially and being a past smoker, and denied illicit drug use. The patient was married with two adult children and worked as a clinical coordinator at a medical institution.

Upon arrival to the ED, the patient was free of chest pain. She was anxious to be examined so she could go back to work. The physical examination was relatively unremarkable. Vital signs were as follows: temperature, 98.1 °F; pulse rate, 76 beats per minute; blood pressure, 148/90 mm Hg; and respiratory rate, 12 to 14 breaths per minute. Notable findings during the examination included a flow murmur, 2/6 systolic ejection murmur, and 2+ pulses throughout with no edema. The patient was hemodynamically stable throughout her time in the ED.

Initial laboratory testing included a complete blood cell count, complete metabolic panel, and cardiac enzymes (creatine kinase, creatine kinase-MB, and cardiac troponin). The patient was given the equivalent of 325 mg of aspirin in chewable form (four 81 mg tablets). A chest x-ray and electrocardiogram (ECG) were also performed.

Initial laboratory test results were essentially unremarkable, with the exception of the cardiac troponin level, which was 0.23 ng/L (upper limit of normal is 0.09 ng/L), reflecting evidence of myonecrosis or ongoing myocardial injury. The creatine kinase and creatine kinase-MB levels were within normal limits which is often the case on initial evaluation. On subsequent evaluations, increases in these levels were observed.

The chest x-ray was essentially unremarkable, with normal lung expansion, no infiltrates or edema, no evidence of cardiomegaly, and no visible vascular calcifications. The initial ECG results revealed nonspecific inferolateral electrical changes: T wave inversion was noted in the inferior leads, and to a lesser degree, the lateral leads. Although not diagnostic for myocardial ischemia, these changes were nonetheless concerning in a patient with no history of atherothrombosis or coronary artery disease.

The patient complained of recurrent chest pain while speaking with the ED physician. She received sublingual nitroglycerin and unfractionated heparin (60 units/kg [5,000 units total]). A repeat ECG was obtained immediately, which showed fairly significant new ST-segment depression (Figure 1).

Diagnosis and management

Based on the symptoms, laboratory test findings, and ECG results, the patient was given a diagnosis of non-ST-segment elevation ACS and was considered to be high risk. She received 600 mg of clopidogrel, which is the standard in both the ED and the catheterization laboratory at our institution, along with i.v. nitroglycerin. The patient reported significant improvement in symptoms shortly thereafter.

The patient then underwent cardiac catheterization. Orthogonal views of the left coronary system clearly revealed a high-grade lesion in the middle of the left anterior descending (LAD) artery (Figure 2). This artery coursed down the anterior wall of the heart and supplied the entire myocardial mass of the anterior wall. Good flow was observed distally, but experience and published data have demonstrated that such lesions are often thrombus-laden, even though this may not be seen angiographically.[1]

Percutaneous coronary intervention (PCI) was performed on the mid-LAD lesion using bivalirudin (direct thrombin inhibition) for procedural anticoagulation. Substantial improvement in flow was observed following balloon inflation. This patient was also studied using intravascular ultrasound technology (Virtual Histology, Volcano Therapeutics, Inc., Rancho Cordova, CA), which provided real-time, in vivo analysis of plaque composition. This study illustrated the presence of significant inflammation and cell death in the plaque at the site of vascular injury. A grayscale adaptation of a cross-sectional, colorized tissue map is provided, revealing areas of necrotic core (Figure 3). Even though this was a very discrete lesion, which from

Figure 1. Repeat electrocardiogram taken during chest pain demonstrating striking ST-segment depression and inferolateral changes (arrows).

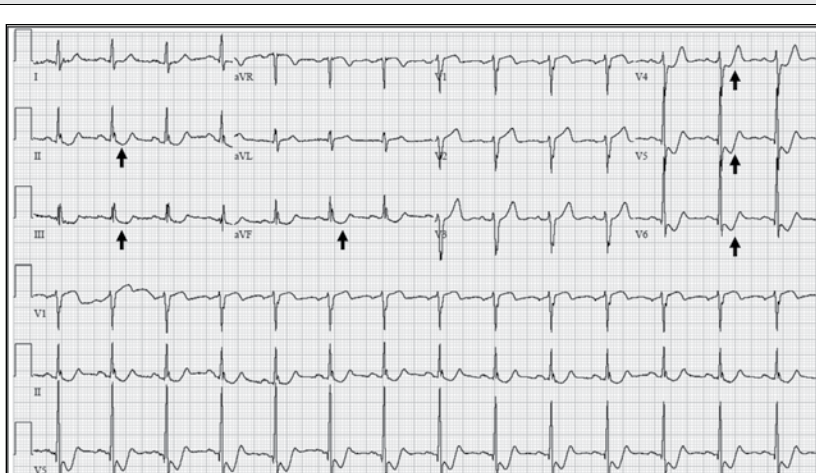


Figure 2. Coronary angiogram shows a highly stenotic lesion in the mid-portion of the left anterior descending artery.

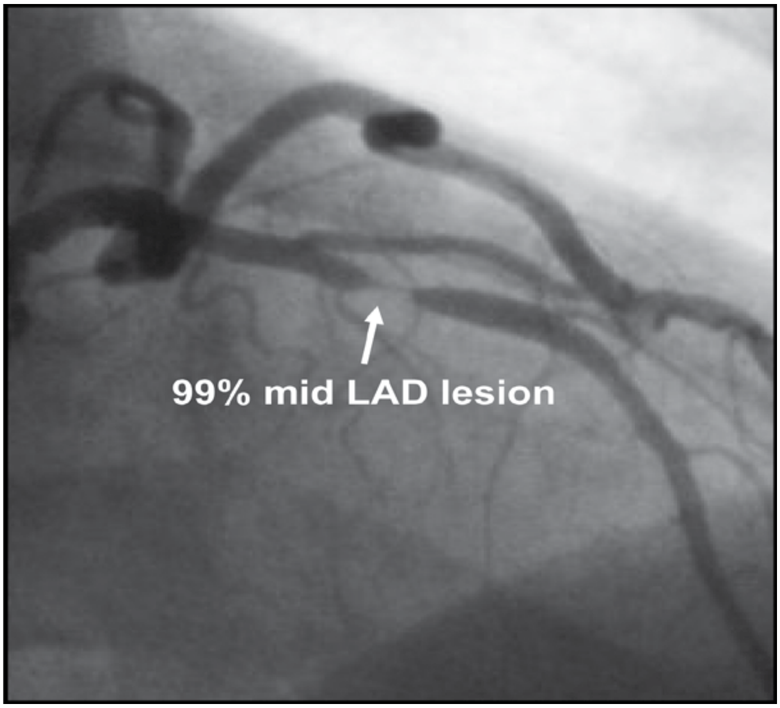
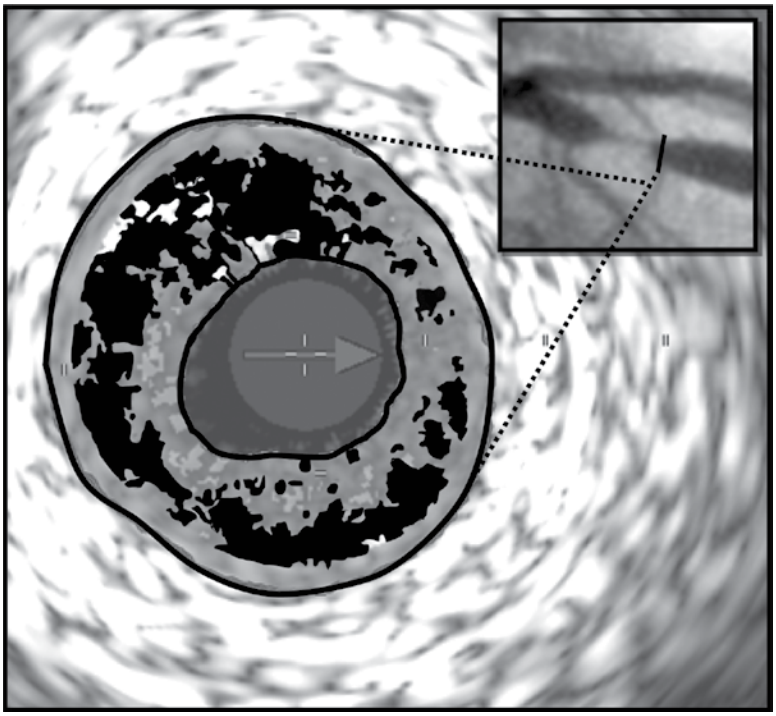


Figure 3. This cross-sectional, intravascular ultrasound-derived tissue map demonstrates significant inflammation and cell death (regions coded black) at the site of plaque rupture, most notably at the "shoulder" of the culprit lesion (inset image).



an interventionalist's perspective was relatively simple and technically straightforward, it bore recognition that the "culprit lesion" required both pharmacologic passivation and device-based reconstruction. A 3.0 x 18 mm drug-eluting stent was implanted in the mid-LAD vessel, and brisk blood flow to the distal territory was observed at the conclusion of the case. In the current U.S. treatment paradigm, drug-eluting stents are often used in patients who have ACS and ST-segment elevation myocardial infarction, with an attendant recommendation of early and sustained (≥ 1 year) dual oral antiplatelet therapy.

Following PCI, rapid peak and fall of cardiac biomarkers were noted and normal cardiac structure and function were observed on ECG. A fasting lipid panel revealed untreated dyslipidemia (total cholesterol, 276 mg/dL; low-density lipoprotein cholesterol, 160 mg/dL; high-density lipoprotein cholesterol, 35 mg/dL; and triglycerides, 98 mg/dL). Statin therapy was prescribed. The patient remained asymptomatic after PCI and was discharged on day 3. She was discharged on the following medications: enteric-coated aspirin (81 mg/day), clopidogrel (75 mg/day), amlodipine (10 mg/day), extended-release metoprolol (50 mg/day), and atorvastatin (80 mg/day). The patient was doing well 6 months after PCI and stent implantation.

Conclusion

Discussion of a patient with non-ST elevation ACS illustrates some of the clinical issues surrounding PCI and stent implantation, including selection and use of antiplatelet therapy.

References

1. Svilaas T, Vlaar PJ, van der Horst IC et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med.* 2008; 358:557-67.

Optimizing antiplatelet therapy in acute coronary syndromes: Balancing efficacy and safety in unstable angina and non-ST-segment elevation myocardial infarction

Article #204-000-10-003-H01P
Knowledge-based activity
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Learning objectives

After studying these articles, the reader should be able to

1. Explain the role of the platelet in thromboembolism and the mechanisms by which the various antiplatelet agents protect against thromboembolic events.
2. Recommend appropriate antiplatelet therapy for a patient with non-ST-segment elevation myocardial infarction (NSTEMI) scheduled for percutaneous coronary intervention (PCI), as recommended by the American College of Cardiology and American Heart Association (ACC/AHA) treatment guidelines.
3. Compare current and emerging oral antiplatelet strategies for long-term protection against risk of thromboembolic events in patients with acute coronary syndromes (ACS), including recommended dosage and duration of therapy.
4. Recognize the complications that can occur in ACS patients post-PCI and determine how to prevent, detect, and manage these events.
5. Describe the methods used to assess antiplatelet effects of oral antiplatelet agents and ways to reduce the rate of platelet resistance.
6. Identify the role of health-system pharmacists in the prevention and management of ACS.

Self-assessment questions

For each question there is only one best answer.

1. The most correct statement about platelet aggregation is
   a. Platelet aggregation is a simple, straightforward process associated with clotting only.
   b. Platelet aggregation is a simple, straightforward process involving inflammation and clotting.
   c. Platelet aggregation is a complex cascade of events involving multiple factors and distinct mechanisms.
   d. Depending on the patient, platelet aggregation can be either a simple, straightforward process involving only clotting or a complex cascade of events involving multiple factors and distinct mechanisms.
2. Following an acute thrombotic event, subendothelial collagen is exposed to the bloodstream, and when platelets come into contact with collagen they
   a. Combine with the collagen and uncontrolled bleeding occurs.
   b. Rapidly multiply and uncontrolled bleeding occurs.
   c. Become activated.
   d. Become inactivated.
3. In patients with ACS, clinical presentation is largely determined by
   a. The extent of thrombosis and the degree of blood flow obstruction.
   b. The age of the patient.
   c. A patient's partial thromboplastin time
   d. The patient's ADP level.
4. Which of the following plays a key role in platelet activation, conformational activation of a variety of other receptors, and mediation of the glycoprotein (GP) IIb/IIIa receptor complex?
   a. Cyclooxygenase (COX)-1 inhibitor.
   b. P2Y12 receptor.
   c. ADP receptor antagonist
   d. GP IIb/IIIa receptor complex.
5. The most correct statement about ticagrelor is that it:
   a. Irreversibly binds to the P2Y12 receptor.
   b. Is a prodrug.
   c. Is a COX-1 inhibitor.
   d. Is a directly active reversible P2Y12 inhibitor.
6. In ACS patients, the gold standard for reducing cardiovascular events has been dual antiplatelet therapy with
   a. Ticlopidine and aspirin.
   b. Clopidogrel and eptifibatide.
   c. Clopidogrel and aspirin.
   d. Cilostazol and aspirin.

7. In ST-segment elevation myocardial infarction (STEMI) patients undergoing planned PCI, the loading dose of prasugrel recommended by the 2009 joint ACC/AHA/SCAI STEMI/PCI focused update guidelines is
   a. 40 mg.
   b. 60 mg.
   c. 150 mg.
   d. 300 mg.
8. In patients undergoing coronary artery bypass grafting, clopidogrel should be withheld for at least
   a. 24 hours.
   b. 48 hours.
   c. 72 hours.
   d. 5 days.
9. Following PCI and placement of a paclitaxel stent, the 2007 ACC/AHA guidelines for the management of unstable angina (UA)/NSTEMI recommend continuation of 162 to 325 mg/day of aspirin for at least
   a. 1 month.
   b. 3 months.
   c. 6 months.
   d. 12 months.
10. Subgroup analyses of the CREDO trial, which evaluated the timing of an oral antiplatelet agent loading dose administration prior to PCI and its impact on patient outcomes, found that
    a. A longer interval between the loading dose and PCI may reduce the incidence of death and ischemic events.
    b. A shorter interval between the loading dose and PCI may reduce the incidence of death and ischemic events.
    c. A longer interval between the loading dose and PCI may reduce the incidence of death but increase the incidence of ischemic events.
    d. A shorter interval between the loading dose and PCI may reduce the incidence of death but increase the incidence of ischemic events.
11. Using clopidogrel at a loading dose of 300 to 600 mg, steady-state levels of platelet aggregation occur within
    a. 1 to 2 hours.
    b. 4 to 24 hours.
    c. 2 to 3 days.
    d. 4 to 7 days.
12. The TRITON-TIMI 38 trial comparing clopidogrel (300 mg loading dose, followed by 75 mg daily) with prasugrel (60 mg loading dose, followed by 10 mg daily) showed that prasugrel produced
    a. Less protection against ischemic events, with more bleeding risk than clopidogrel.
    b. Similar protection against ischemic events and less bleeding risk than clopidogrel.
    c. Greater protection against ischemic events, with less bleeding risk than clopidogrel.
    d. Greater protection against ischemic events, with more bleeding risk than clopidogrel.
13. The ongoing TRILOGY ACS study is recruiting patients to evaluate the relative efficacy and safety of
    a. Prasugrel (30 mg loading dose, 5 or 10 mg/day maintenance dosage) and clopidogrel (300 mg loading dose, 75 mg/day maintenance dosage).
    b. Prasugrel (40 mg loading dose, 15 mg/day maintenance dosage) and clopidogrel (600 mg loading dose, 150 mg/day maintenance dosage).
    c. Ticagrelor (25 mg loading dose, 10 mg/day maintenance dosage) and clopidogrel (300 mg loading dose, 75 mg/day maintenance dosage).
    d. Ticagrelor (40 mg loading dose, 10 mg/day maintenance dosage) and clopidogrel (600 mg loading dose, 150 mg/day maintenance dosage).
14. The PLATO trial compared the investigational drug ticagrelor with
    a. Cilostazol.
    b. Clopidogrel.
    c. Prasugrel.
    d. Eptifibatide.
15. Which of the following factors has been associated with the highest rate of stent thrombosis in a patient with ACS who received a drug-eluting stent during PCI?
    a. Renal failure.
    b. Diabetes mellitus.
    c. Premature antiplatelet discontinuation.
    d. Unstable angina.
16. The most correct statement regarding the metabolism of prasugrel is:
    a. One cytochrome P450 (CYP)-dependent oxidation step that involves various CYP isoenzymes is required to generate the active compound of prasugrel.
    b. A two-step process that involves the CYP2B6 isoenzyme is required to generate the active compound of prasugrel.
    c. A two-step process that involves a variety of CYP isoenzymes is required to generate the active compound of prasugrel.
    d. A three-step process that involves the CYP2C19, CYP3A4, and CYP2B6 isoenzymes is required to generate the active compound of prasugrel.
17. The most correct statement regarding the effect of clopidogrel dosing on the rate of hyporesponsiveness is that:
    a. The rate of hyporesponsiveness is not affected by the dose of clopidogrel.
    b. The rate of hyporesponsiveness is lower with a 600 mg loading dose compared with a 300 mg loading dose.

c. The rate of hyporesponsiveness is significantly lower with a 300 mg loading dose compared with a 600 mg loading dose.
d. The rate of hyporesponsiveness is only affected when low-dose clopidogrel (150 mg) is used in combination with a GP IIb/IIIa inhibitor.

18. With the P2Y12 point-of-care assay, which of the following agonists is used to induce platelet activation and determine the level of platelet reactivity impairment?
a. VASP.
b. GP IIb/IIIa.
c. Collagen.
d. ADP.

19. The wild type *CYP2C19*1/*1* allele, which is associated with a higher degree of extensive metabolic activation, has been found with greater frequency in which ethnicity?
a. Caucasians.
b. Native Americans.
c. African Americans.
d. Asians.

20. Concomitant use of clopidogrel and a CYP2C19 inhibitor may
a. Augment the antiplatelet effects of clopidogrel.
b. Augment the effects of the CYP2C19 inhibitor.
c. Attenuate the antiplatelet effects of clopidogrel.
d. Attenuate the effects of the CYP2C19 inhibitor.

AJHP Continuing Education

Supplement: **Optimizing antiplatelet therapy in acute coronary syndromes: Balancing efficacy and safety in unstable angina and non-ST-segment elevation myocardial infarction**

ACPE #: 204-000-10-003-H01P
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